```
     (FILE 'HOME' ENTERED AT 13:30:58 ON 06 JUN 2003)

     FILE 'USPATFULL, CAPLUS' ENTERED AT 13:31:19 ON 06 JUN 2003
L1          1547 FILE USPATFULL
L2          7069 FILE CAPLUS
     TOTAL FOR ALL FILES
L3          8616 S COX-2 OR COX2 OR CYCLOOXYGENASE-2 OR CYCLOOXYGENASE2 OR CYCLO
L4           454 FILE USPATFULL
L5           573 FILE CAPLUS
     TOTAL FOR ALL FILES
L6          1027 S 162011-90-7/RN OR 162011-90-7 OR ROFECOXIB OR VIOXX OR (MK 09
L7           576 FILE USPATFULL
L8           745 FILE CAPLUS
     TOTAL FOR ALL FILES
L9          1321 S CELECOXIB OR CELEBREX OR (SC58635) OR (SC58635) OR (SC-58635)
L10          454 FILE USPATFULL
L11          573 FILE CAPLUS
     TOTAL FOR ALL FILES
L12         1027 S 162011-90-7/RN OR 162011-90-7 OR ROFECOXIB OR VIOXX OR (MK 09
L13          579 FILE USPATFULL
L14          745 FILE CAPLUS
     TOTAL FOR ALL FILES
L15         1324 S CELECOXIB OR CELEBREX OR (SC58635) OR (SC58635) OR (SC-58635)
L16             1 FILE USPATFULL
L17             1 FILE CAPLUS
     TOTAL FOR ALL FILES
L18             2 S ACUTE MUCOSAL EFFECT
L19             9 FILE USPATFULL
L20            53 FILE CAPLUS
     TOTAL FOR ALL FILES
L21            62 S (ACUTE (4A) MUCOSAL (4A)  EFFECT?)
L22         57401 FILE USPATFULL
L23         74424 FILE CAPLUS
     TOTAL FOR ALL FILES
L24        131825 S FATIGUE
L25          7764 FILE USPATFULL
L26         13345 FILE CAPLUS
     TOTAL FOR ALL FILES
L27         21109 S DIARRHEA
L28          7811 FILE USPATFULL
L29         13412 FILE CAPLUS
     TOTAL FOR ALL FILES
L30         21223 S DIARRHEA OR (LOOSE STOOL)
L31           163 FILE USPATFULL
L32            53 FILE CAPLUS
     TOTAL FOR ALL FILES
L33           216 S (RECTAL BLEEDING)
L34           715 FILE USPATFULL
L35            95 FILE CAPLUS
     TOTAL FOR ALL FILES
L36           810 S PROCTITIS
L37           774 FILE USPATFULL
L38           198 FILE CAPLUS
     TOTAL FOR ALL FILES
L39           972 S PROCTITIS OR (INFLAMMATION  (3A) (RECTUM OR RECTAL))
L40           786 FILE USPATFULL
L41           202 FILE CAPLUS
     TOTAL FOR ALL FILES
L42           988 S PROCTITIS OR (INFLAMMATION  (3A) (RECTUM OR RECTAL OR ANUS OR
L43            12 FILE USPATFULL
L44             3 FILE CAPLUS
     TOTAL FOR ALL FILES
L45            15 S SIGMOIDITIS OR (INHLAMMATION (4A) SIGMOID? (4A) COLON)
```

```
L46          12 FILE USPATFULL
L47           3 FILE CAPLUS
     TOTAL FOR ALL FILES
L48          15 S SIGMOIDITIS OR (INHLAMMATION (4A) SIGMOID? (4A) (INTERSTINE O
L49          16 FILE USPATFULL
L50           3 FILE CAPLUS
     TOTAL FOR ALL FILES
L51          19 S SIGMOIDITIS OR (INFLAMMATION (4A) SIGMOID? (4A) (INTERSTINE O
L52          16 FILE USPATFULL
L53           3 FILE CAPLUS
     TOTAL FOR ALL FILES
L54          19 S SIGMOIDITIS OR (INFLAMMATION (4A) SIGMOID? (4A) (INTESTINE OR
L55        1023 FILE USPATFULL
L56         600 FILE CAPLUS
     TOTAL FOR ALL FILES
L57        1623 S PROSTATITIS OR (INFLAMMATION (5A) PROSTATE)
L58        1569 FILE USPATFULL
L59        1108 FILE CAPLUS
     TOTAL FOR ALL FILES
L60        2677 S CYSTITIS OR (INFLAMMATION (5A) BLADDER)
L61       11019 FILE USPATFULL
L62       13518 FILE CAPLUS
     TOTAL FOR ALL FILES
L63       24537 S DERMATITIS OR (INFLAMMATION (5A) SKIN)
L64         437 FILE USPATFULL
L65         426 FILE CAPLUS
     TOTAL FOR ALL FILES
L66         863 S (URINARY (3A) FREQUEN?)
L67           2 FILE USPATFULL
L68           5 FILE CAPLUS
     TOTAL FOR ALL FILES
L69           7 S L21 (1S) TREAT?
L70        5238 FILE USPATFULL
L71        8341 FILE CAPLUS
     TOTAL FOR ALL FILES
L72       13579 S L24 (1S) TREAT?
L73        3578 FILE USPATFULL
L74        3160 FILE CAPLUS
     TOTAL FOR ALL FILES
L75        6738 S L30 (1S) TREAT?
L76          79 FILE USPATFULL
L77          18 FILE CAPLUS
     TOTAL FOR ALL FILES
L78          97 S L33 (1S) TREAT?
L79         476 FILE USPATFULL
L80         102 FILE CAPLUS
     TOTAL FOR ALL FILES
L81         578 S L42 (1S) TREAT?
L82           7 FILE USPATFULL
L83           2 FILE CAPLUS
     TOTAL FOR ALL FILES
L84           9 S L51 (1S) TREAT?
L85         677 FILE USPATFULL
L86         267 FILE CAPLUS
     TOTAL FOR ALL FILES
L87         944 S L57 (1S) TREAT?
L88         882 FILE USPATFULL
L89         386 FILE CAPLUS
     TOTAL FOR ALL FILES
L90        1268 S L60 (1S) TREAT?
L91        7480 FILE USPATFULL
L92        3288 FILE CAPLUS
     TOTAL FOR ALL FILES
L93       10768 S L63 (1S) TREAT?
```

```
L94          156 FILE USPATFULL
L95          191 FILE CAPLUS
     TOTAL FOR ALL FILES
L96          347 S L66 (1S) TREAT?
L97          625 FILE USPATFULL
L98          989 FILE CAPLUS
     TOTAL FOR ALL FILES
L99         1614 S L12 OR L15
L100           0 FILE USPATFULL
L101           0 FILE CAPLUS
     TOTAL FOR ALL FILES
L102           0 S L99 (3S) L69
L103           3 FILE USPATFULL
L104           1 FILE CAPLUS
     TOTAL FOR ALL FILES
L105           4 S L99 (3S) L72
L106           1 FILE USPATFULL
L107           4 FILE CAPLUS
     TOTAL FOR ALL FILES
L108           5 S L99 (3S) L75
L109           0 FILE USPATFULL
L110           1 FILE CAPLUS
     TOTAL FOR ALL FILES
L111           1 S L99 (3S) L81
L112           0 FILE USPATFULL
L113           0 FILE CAPLUS
     TOTAL FOR ALL FILES
L114           0 S L99 (3S) L84
L115           1 FILE USPATFULL
L116           2 FILE CAPLUS
     TOTAL FOR ALL FILES
L117           3 S L99 (3S) L87
L118           0 FILE USPATFULL
L119           0 FILE CAPLUS
     TOTAL FOR ALL FILES
L120           0 S L99 (3S) L90
L121           0 FILE USPATFULL
L122           8 FILE CAPLUS
     TOTAL FOR ALL FILES
L123           8 S L99 (3S) L93
L124           0 FILE USPATFULL
L125           0 FILE CAPLUS
     TOTAL FOR ALL FILES
L126           0 S L99 (3S) L96
L127         625 FILE USPATFULL
L128           5 FILE USPATFULL
L129           9 FILE USPATFULL
L130          25 FILE CAPLUS
     TOTAL FOR ALL FILES
L131          34 S L21 AND TREAT?
L132       19027 FILE USPATFULL
L133       11676 FILE CAPLUS
     TOTAL FOR ALL FILES
L134       30703 S L24 AND TREAT?
L135        7445 FILE USPATFULL
L136        5127 FILE CAPLUS
     TOTAL FOR ALL FILES
L137       12572 S L30 AND TREAT?
L138         160 FILE USPATFULL
L139          30 FILE CAPLUS
     TOTAL FOR ALL FILES
L140         190 S L33 AND TREAT?
L141         779 FILE USPATFULL
L142         134 FILE CAPLUS
```

```
     TOTAL FOR ALL FILES
L143         913 S L42 AND TREAT?
L144          16 FILE USPATFULL
L145           3 FILE CAPLUS
     TOTAL FOR ALL FILES
L146          19 S L51 AND TREAT?
L147         997 FILE USPATFULL
L148         330 FILE CAPLUS
     TOTAL FOR ALL FILES
L149        1327 S L57  AND TREAT?
L150        1524 FILE USPATFULL
L151         558 FILE CAPLUS
     TOTAL FOR ALL FILES
L152        2082 S L60  AND TREAT?
L153       10661 FILE USPATFULL
L154        5030 FILE CAPLUS
     TOTAL FOR ALL FILES
L155       15691 S L63  AND TREAT?
L156         414 FILE USPATFULL
L157         258 FILE CAPLUS
     TOTAL FOR ALL FILES
L158         672 S L66  AND TREAT?
L159           1 FILE USPATFULL
L160           1 FILE CAPLUS
     TOTAL FOR ALL FILES
L161           2 S L131 AND L99
L162          58 FILE USPATFULL
L163           2 FILE CAPLUS
     TOTAL FOR ALL FILES
L164          60 S L134 AND L99
L165          68 FILE USPATFULL
L166          10 FILE CAPLUS
     TOTAL FOR ALL FILES
L167          78 S L137 AND L99
L168           8 FILE USPATFULL
L169           0 FILE CAPLUS
     TOTAL FOR ALL FILES
L170           8 S L140 AND L99
L171           5 FILE USPATFULL
L172           2 FILE CAPLUS
     TOTAL FOR ALL FILES
L173           7 S L143 AND L99
L174           1 FILE USPATFULL
L175           1 FILE CAPLUS
     TOTAL FOR ALL FILES
L176           2 S L146 AND L99
L177          15 FILE USPATFULL
L178           3 FILE CAPLUS
     TOTAL FOR ALL FILES
L179          18 S L149 AND L99
L180          17 FILE USPATFULL
L181           1 FILE CAPLUS
     TOTAL FOR ALL FILES
L182          18 S L152 AND L99
L183         174 FILE USPATFULL
L184          16 FILE CAPLUS
     TOTAL FOR ALL FILES
L185         190 S L155 AND L99
L186           4 FILE USPATFULL
L187           0 FILE CAPLUS
     TOTAL FOR ALL FILES
L188           4 S L158 AND L99
L189         241 FILE USPATFULL
L190          29 FILE CAPLUS
```

```
     TOTAL FOR ALL FILES
L191          270 S L159-L188
L192        75708 FILE USPATFULL
L193       103192 FILE CAPLUS
     TOTAL FOR ALL FILES
L194       178900 S L21 OR L24 OR L30 OR L33 OR L42 OR L51 OR L57 OR L60 OR L63 O
L195            8 FILE USPATFULL
L196           35 FILE CAPLUS
     TOTAL FOR ALL FILES
L197           43 S L194 (2S) L99
L198            7 FILE USPATFULL
L199           29 FILE CAPLUS
     TOTAL FOR ALL FILES
L200           36 S L197 AND L191
```

```
     FILE 'USPATFULL, CAPLUS' ENTERED AT 13:31:19 ON 06 JUN 2003
L1          1547 FILE USPATFULL
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     TOTAL FOR ALL FILES
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     TOTAL FOR ALL FILES
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L12         1027 S 162011-90-7/RN OR 162011-90-7 OR ROFECOXIB OR VIOXX OR (MK 09
L13          579 FILE USPATFULL
L14          745 FILE CAPLUS
     TOTAL FOR ALL FILES
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L16            1 FILE USPATFULL
L17            1 FILE CAPLUS
     TOTAL FOR ALL FILES
L18            2 S ACUTE MUCOSAL EFFECT
L19            9 FILE USPATFULL
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     TOTAL FOR ALL FILES
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L22        57401 FILE USPATFULL
L23        74424 FILE CAPLUS
     TOTAL FOR ALL FILES
L24       131825 S FATIGUE
L25         7764 FILE USPATFULL
L26        13345 FILE CAPLUS
     TOTAL FOR ALL FILES
L27        21109 S DIARRHEA
L28         7811 FILE USPATFULL
L29        13412 FILE CAPLUS
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L30        21223 S DIARRHEA OR (LOOSE STOOL)
L31          163 FILE USPATFULL
L32           53 FILE CAPLUS
     TOTAL FOR ALL FILES
L33          216 S (RECTAL BLEEDING)
L34          715 FILE USPATFULL
L35           95 FILE CAPLUS
     TOTAL FOR ALL FILES
L36          810 S PROCTITIS
L37          774 FILE USPATFULL
L38          198 FILE CAPLUS
     TOTAL FOR ALL FILES
L39          972 S PROCTITIS OR (INFLAMMATION  (3A) (RECTUM OR RECTAL))
L40          786 FILE USPATFULL
L41          202 FILE CAPLUS
     TOTAL FOR ALL FILES
L42          988 S PROCTITIS OR (INFLAMMATION  (3A) (RECTUM OR RECTAL OR ANUS OR
L43           12 FILE USPATFULL
L44            3 FILE CAPLUS
     TOTAL FOR ALL FILES
L45           15 S SIGMOIDITIS OR (INHLAMMATION (4A) SIGMOID? (4A) COLON)
L46           12 FILE USPATFULL
L47            3 FILE CAPLUS
```

```
     TOTAL FOR ALL FILES
L48           15 S SIGMOIDITIS OR (INHLAMMATION (4A) SIGMOID? (4A) (INTERSTINE O
L49           16 FILE USPATFULL
L50            3 FILE CAPLUS
     TOTAL FOR ALL FILES
L51           19 S SIGMOIDITIS OR (INFLAMMATION (4A) SIGMOID? (4A) (INTERSTINE O
L52           16 FILE USPATFULL
L53            3 FILE CAPLUS
     TOTAL FOR ALL FILES
L54           19 S SIGMOIDITIS OR (INFLAMMATION (4A) SIGMOID? (4A) (INTESTINE OR
L55         1023 FILE USPATFULL
L56          600 FILE CAPLUS
     TOTAL FOR ALL FILES
L57         1623 S PROSTATITIS OR (INFLAMMATION (5A) PROSTATE)
L58         1569 FILE USPATFULL
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     TOTAL FOR ALL FILES
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L62        13518 FILE CAPLUS
     TOTAL FOR ALL FILES
L63        24537 S DERMATITIS OR (INFLAMMATION (5A) SKIN)
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     TOTAL FOR ALL FILES
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L67            2 FILE USPATFULL
L68            5 FILE CAPLUS
     TOTAL FOR ALL FILES
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L71         8341 FILE CAPLUS
     TOTAL FOR ALL FILES
L72        13579 S L24 (1S) TREAT?
L73         3578 FILE USPATFULL
L74         3160 FILE CAPLUS
     TOTAL FOR ALL FILES
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L76           79 FILE USPATFULL
L77           18 FILE CAPLUS
     TOTAL FOR ALL FILES
L78           97 S L33 (1S) TREAT?
L79          476 FILE USPATFULL
L80          102 FILE CAPLUS
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     TOTAL FOR ALL FILES
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L86          267 FILE CAPLUS
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L88          882 FILE USPATFULL
L89          386 FILE CAPLUS
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L91         7480 FILE USPATFULL
L92         3288 FILE CAPLUS
     TOTAL FOR ALL FILES
L93        10768 S L63 (1S) TREAT?
L94          156 FILE USPATFULL
L95          191 FILE CAPLUS
```

```
     TOTAL FOR ALL FILES
L96          347 S L66 (1S) TREAT?
L97          625 FILE USPATFULL
L98          989 FILE CAPLUS
     TOTAL FOR ALL FILES
L99         1614 S L12 OR L15
L100           0 FILE USPATFULL
L101           0 FILE CAPLUS
     TOTAL FOR ALL FILES
L102           0 S L99 (3S) L69
L103           3 FILE USPATFULL
L104           1 FILE CAPLUS
     TOTAL FOR ALL FILES
L105           4 S L99 (3S) L72
L106           1 FILE USPATFULL
L107           4 FILE CAPLUS
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L109           0 FILE USPATFULL
L110           1 FILE CAPLUS
     TOTAL FOR ALL FILES
L111           1 S L99 (3S) L81
L112           0 FILE USPATFULL
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     TOTAL FOR ALL FILES
L114           0 S L99 (3S) L84
L115           1 FILE USPATFULL
L116           2 FILE CAPLUS
     TOTAL FOR ALL FILES
L117           3 S L99 (3S) L87
L118           0 FILE USPATFULL
L119           0 FILE CAPLUS
     TOTAL FOR ALL FILES
L120           0 S L99 (3S) L90
L121           0 FILE USPATFULL
L122           8 FILE CAPLUS
     TOTAL FOR ALL FILES
L123           8 S L99 (3S) L93
L124           0 FILE USPATFULL
L125           0 FILE CAPLUS
     TOTAL FOR ALL FILES
L126           0 S L99 (3S) L96
L127         625 FILE USPATFULL
L128           5 FILE USPATFULL
L129           9 FILE USPATFULL
L130          25 FILE CAPLUS
     TOTAL FOR ALL FILES
L131          34 S L21 AND TREAT?
L132       19027 FILE USPATFULL
L133       11676 FILE CAPLUS
     TOTAL FOR ALL FILES
L134       30703 S L24 AND TREAT?
L135        7445 FILE USPATFULL
L136        5127 FILE CAPLUS
     TOTAL FOR ALL FILES
L137       12572 S L30 AND TREAT?
L138         160 FILE USPATFULL
L139          30 FILE CAPLUS
     TOTAL FOR ALL FILES
L140         190 S L33 AND TREAT?
L141         779 FILE USPATFULL
L142         134 FILE CAPLUS
     TOTAL FOR ALL FILES
L143         913 S L42 AND TREAT?
```

```
L144          16 FILE USPATFULL
L145           3 FILE CAPLUS
     TOTAL FOR ALL FILES
L146          19 S L51 AND TREAT?
L147         997 FILE USPATFULL
L148         330 FILE CAPLUS
     TOTAL FOR ALL FILES
L149        1327 S L57  AND TREAT?
L150        1524 FILE USPATFULL
L151         558 FILE CAPLUS
     TOTAL FOR ALL FILES
L152        2082 S L60  AND TREAT?
L153       10661 FILE USPATFULL
L154        5030 FILE CAPLUS
     TOTAL FOR ALL FILES
L155       15691 S L63  AND TREAT?
L156         414 FILE USPATFULL
L157         258 FILE CAPLUS
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L160           1 FILE CAPLUS
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L166          10 FILE CAPLUS
     TOTAL FOR ALL FILES
L167          78 S L137 AND L99
L168           8 FILE USPATFULL
L169           0 FILE CAPLUS
     TOTAL FOR ALL FILES
L170           8 S L140 AND L99
L171           5 FILE USPATFULL
L172           2 FILE CAPLUS
     TOTAL FOR ALL FILES
L173           7 S L143 AND L99
L174           1 FILE USPATFULL
L175           1 FILE CAPLUS
     TOTAL FOR ALL FILES
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L177          15 FILE USPATFULL
L178           3 FILE CAPLUS
     TOTAL FOR ALL FILES
L179          18 S L149 AND L99
L180          17 FILE USPATFULL
L181           1 FILE CAPLUS
     TOTAL FOR ALL FILES
L182          18 S L152 AND L99
L183         174 FILE USPATFULL
L184          16 FILE CAPLUS
     TOTAL FOR ALL FILES
L185         190 S L155 AND L99
L186           4 FILE USPATFULL
L187           0 FILE CAPLUS
     TOTAL FOR ALL FILES
L188           4 S L158 AND L99
L189         241 FILE USPATFULL
L190          29 FILE CAPLUS
     TOTAL FOR ALL FILES
L191         270 S L159-L188
```

```
L192       75708 FILE USPATFULL
L193      103192 FILE CAPLUS
     TOTAL FOR ALL FILES
L194      178900 S L21 OR L24 OR L30 OR L33 OR L42 OR L51 OR L57 OR L60 OR L63 O
L195           8 FILE USPATFULL
L196          35 FILE CAPLUS
     TOTAL FOR ALL FILES
L197          43 S L194 (2S) L99
L198           7 FILE USPATFULL
L199          29 FILE CAPLUS
     TOTAL FOR ALL FILES
L200          36 S L197 AND L191

=> sace all
SACE IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).

=> save all
ENTER NAME OR (END):cox2rad/l
L# LIST L1-L200 HAS BEEN SAVED AS 'COX2RAD/L'
```

```
=> save all
ENTER NAME OR (END):cox2rad/l
L# LIST L1-L200 HAS BEEN SAVED AS 'COX2RAD/L'

=> d his

     (FILE 'HOME' ENTERED AT 13:30:58 ON 06 JUN 2003)

     FILE 'USPATFULL, CAPLUS' ENTERED AT 13:31:19 ON 06 JUN 2003
L1          1547 FILE USPATFULL
L2          7069 FILE CAPLUS
     TOTAL FOR ALL FILES
L3          8616 S COX-2 OR COX2 OR CYCLOOXYGENASE-2 OR CYCLOOXYGENASE2 OR CYCLO
L4           454 FILE USPATFULL
L5           573 FILE CAPLUS
     TOTAL FOR ALL FILES
L6          1027 S 162011-90-7/RN OR 162011-90-7 OR ROFECOXIB OR VIOXX OR (MK 09
L7           576 FILE USPATFULL
L8           745 FILE CAPLUS
     TOTAL FOR ALL FILES
L9          1321 S CELECOXIB OR CELEBREX OR (SC58635) OR (SC58635) OR (SC-58635)
L10          454 FILE USPATFULL
L11          573 FILE CAPLUS
     TOTAL FOR ALL FILES
L12         1027 S 162011-90-7/RN OR 162011-90-7 OR ROFECOXIB OR VIOXX OR (MK 09
L13          579 FILE USPATFULL
L14          745 FILE CAPLUS
     TOTAL FOR ALL FILES
L15         1324 S CELECOXIB OR CELEBREX OR (SC58635) OR (SC58635) OR (SC-58635)
L16            1 FILE USPATFULL
L17            1 FILE CAPLUS
     TOTAL FOR ALL FILES
L18            2 S ACUTE MUCOSAL EFFECT
L19            9 FILE USPATFULL
L20           53 FILE CAPLUS
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L22        57401 FILE USPATFULL
L23        74424 FILE CAPLUS
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L26        13345 FILE CAPLUS
     TOTAL FOR ALL FILES
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L28         7811 FILE USPATFULL
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L30        21223 S DIARRHEA OR (LOOSE STOOL)
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L32           53 FILE CAPLUS
     TOTAL FOR ALL FILES
L33          216 S (RECTAL BLEEDING)
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L35           95 FILE CAPLUS
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L37          774 FILE USPATFULL
L38          198 FILE CAPLUS
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L39          972 S PROCTITIS OR (INFLAMMATION  (3A) (RECTUM OR RECTAL))
L40          786 FILE USPATFULL
L41          202 FILE CAPLUS
     TOTAL FOR ALL FILES
```

```
L42          988 S PROCTITIS OR (INFLAMMATION  (3A) (RECTUM OR RECTAL OR ANUS OR
L43           12 FILE USPATFULL
L44            3 FILE CAPLUS
     TOTAL FOR ALL FILES
L45           15 S SIGMOIDITIS OR (INHLAMMATION (4A) SIGMOID? (4A) COLON)
L46           12 FILE USPATFULL
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L50            3 FILE CAPLUS
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L54           19 S SIGMOIDITIS OR (INFLAMMATION (4A) SIGMOID? (4A) (INTESTINE OR
L55         1023 FILE USPATFULL
L56          600 FILE CAPLUS
     TOTAL FOR ALL FILES
L57         1623 S PROSTATITIS OR (INFLAMMATION (5A) PROSTATE)
L58         1569 FILE USPATFULL
L59         1108 FILE CAPLUS
     TOTAL FOR ALL FILES
L60         2677 S CYSTITIS OR (INFLAMMATION (5A) BLADDER)
L61        11019 FILE USPATFULL
L62        13518 FILE CAPLUS
     TOTAL FOR ALL FILES
L63        24537 S DERMATITIS OR (INFLAMMATION (5A) SKIN)
L64          437 FILE USPATFULL
L65          426 FILE CAPLUS
     TOTAL FOR ALL FILES
L66          863 S (URINARY (3A) FREQUEN?)
L67            2 FILE USPATFULL
L68            5 FILE CAPLUS
     TOTAL FOR ALL FILES
L69            7 S L21 (1S) TREAT?
L70         5238 FILE USPATFULL
L71         8341 FILE CAPLUS
     TOTAL FOR ALL FILES
L72        13579 S L24 (1S) TREAT?
L73         3578 FILE USPATFULL
L74         3160 FILE CAPLUS
     TOTAL FOR ALL FILES
L75         6738 S L30 (1S) TREAT?
L76           79 FILE USPATFULL
L77           18 FILE CAPLUS
     TOTAL FOR ALL FILES
L78           97 S L33 (1S) TREAT?
L79          476 FILE USPATFULL
L80          102 FILE CAPLUS
     TOTAL FOR ALL FILES
L81          578 S L42 (1S) TREAT?
L82            7 FILE USPATFULL
L83            2 FILE CAPLUS
     TOTAL FOR ALL FILES
L84            9 S L51 (1S) TREAT?
L85          677 FILE USPATFULL
L86          267 FILE CAPLUS
     TOTAL FOR ALL FILES
L87          944 S L57 (1S) TREAT?
L88          882 FILE USPATFULL
L89          386 FILE CAPLUS
     TOTAL FOR ALL FILES
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L90         1268 S L60 (1S) TREAT?
L91         7480 FILE USPATFULL
L92         3288 FILE CAPLUS
     TOTAL FOR ALL FILES
L93        10768 S L63 (1S) TREAT?
L94          156 FILE USPATFULL
L95          191 FILE CAPLUS
     TOTAL FOR ALL FILES
L96          347 S L66 (1S) TREAT?
L97          625 FILE USPATFULL
L98          989 FILE CAPLUS
     TOTAL FOR ALL FILES
L99         1614 S L12 OR L15
L100           0 FILE USPATFULL
L101           0 FILE CAPLUS
     TOTAL FOR ALL FILES
L102           0 S L99 (3S) L69
L103           3 FILE USPATFULL
L104           1 FILE CAPLUS
     TOTAL FOR ALL FILES
L105           4 S L99 (3S) L72
L106           1 FILE USPATFULL
L107           4 FILE CAPLUS
     TOTAL FOR ALL FILES
L108           5 S L99 (3S) L75
L109           0 FILE USPATFULL
L110           1 FILE CAPLUS
     TOTAL FOR ALL FILES
L111           1 S L99 (3S) L81
L112           0 FILE USPATFULL
L113           0 FILE CAPLUS
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L114           0 S L99 (3S) L84
L115           1 FILE USPATFULL
L116           2 FILE CAPLUS
     TOTAL FOR ALL FILES
L117           3 S L99 (3S) L87
L118           0 FILE USPATFULL
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L123           8 S L99 (3S) L93
L124           0 FILE USPATFULL
L125           0 FILE CAPLUS
     TOTAL FOR ALL FILES
L126           0 S L99 (3S) L96
L127         625 FILE USPATFULL
L128           5 FILE USPATFULL
L129           9 FILE USPATFULL
L130          25 FILE CAPLUS
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L131          34 S L21 AND TREAT?
L132       19027 FILE USPATFULL
L133       11676 FILE CAPLUS
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L134       30703 S L24 AND TREAT?
L135        7445 FILE USPATFULL
L136        5127 FILE CAPLUS
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L137       12572 S L30 AND TREAT?
L138         160 FILE USPATFULL
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L139          30 FILE CAPLUS
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L140         190 S L33 AND TREAT?
L141         779 FILE USPATFULL
L142         134 FILE CAPLUS
     TOTAL FOR ALL FILES
L143         913 S L42 AND TREAT?
L144          16 FILE USPATFULL
L145           3 FILE CAPLUS
     TOTAL FOR ALL FILES
L146          19 S L51 AND TREAT?
L147         997 FILE USPATFULL
L148         330 FILE CAPLUS
     TOTAL FOR ALL FILES
L149        1327 S L57  AND TREAT?
L150        1524 FILE USPATFULL
L151         558 FILE CAPLUS
     TOTAL FOR ALL FILES
L152        2082 S L60  AND TREAT?
L153       10661 FILE USPATFULL
L154        5030 FILE CAPLUS
     TOTAL FOR ALL FILES
L155       15691 S L63  AND TREAT?
L156         414 FILE USPATFULL
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     TOTAL FOR ALL FILES
L158         672 S L66  AND TREAT?
L159           1 FILE USPATFULL
L160           1 FILE CAPLUS
     TOTAL FOR ALL FILES
L161           2 S L131 AND L99
L162          58 FILE USPATFULL
L163           2 FILE CAPLUS
     TOTAL FOR ALL FILES
L164          60 S L134 AND L99
L165          68 FILE USPATFULL
L166          10 FILE CAPLUS
     TOTAL FOR ALL FILES
L167          78 S L137 AND L99
L168           8 FILE USPATFULL
L169           0 FILE CAPLUS
     TOTAL FOR ALL FILES
L170           8 S L140 AND L99
L171           5 FILE USPATFULL
L172           2 FILE CAPLUS
     TOTAL FOR ALL FILES
L173           7 S L143 AND L99
L174           1 FILE USPATFULL
L175           1 FILE CAPLUS
     TOTAL FOR ALL FILES
L176           2 S L146 AND L99
L177          15 FILE USPATFULL
L178           3 FILE CAPLUS
     TOTAL FOR ALL FILES
L179          18 S L149 AND L99
L180          17 FILE USPATFULL
L181           1 FILE CAPLUS
     TOTAL FOR ALL FILES
L182          18 S L152 AND L99
L183         174 FILE USPATFULL
L184          16 FILE CAPLUS
     TOTAL FOR ALL FILES
L185         190 S L155 AND L99
L186           4 FILE USPATFULL
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L187          0 FILE CAPLUS
     TOTAL FOR ALL FILES
L188          4 S L158 AND L99
L189        241 FILE USPATFULL
L190         29 FILE CAPLUS
     TOTAL FOR ALL FILES
L191        270 S L159-L188
L192      75708 FILE USPATFULL
L193     103192 FILE CAPLUS
     TOTAL FOR ALL FILES
L194     178900 S L21 OR L24 OR L30 OR L33 OR L42 OR L51 OR L57 OR L60 OR L63 O
L195          8 FILE USPATFULL
L196         35 FILE CAPLUS
     TOTAL FOR ALL FILES
L197         43 S L194 (2S) L99
L198          7 FILE USPATFULL
L199         29 FILE CAPLUS
     TOTAL FOR ALL FILES
L200         36 S L197 AND L191
                SAVE ALL COX2RAD/L
```

L200 ANSWER 28 OF 36 CAPLUS COPYRIGHT 2003 ACS
AN 2001:904209 CAPLUS
DN 136:31724
TI Heterocycle derivatives and methods of use
IN Peterson, Johnny W.; Gessell-Lee, Deborah L.; Saini, Shamsher S.
PA The University of Texas System, USA
SO PCT Int. Appl., 88 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C07H019-20
CC 1-12 (Pharmacology)
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2001094369	A2	20011213	WO 2001-US16190	20010519
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 2002032228	A1	20020314	US 2001-860652	20010519
US 20020188016	A9	20021212		
PRAI US 2000-210412P	P	20000608		

OS MARPAT 136:31724
AB The present invention provides methods for **treating** intestinal fluid loss, whooping cough, anthrax, and conditions assocd. with smooth muscle contraction. The present invention also provides methods for inhibiting adenylate cyclase in vivo and in vitro.
ST heterocycle deriv adenylate cyclase inhibition **diarrhea**; intestinal fluid loss **treatment** heterocycle deriv; smooth muscle contraction inhibition heterocycle deriv; whooping cough **treatment** heterocycle deriv
IT Animal cell
(adenylate cyclase-contg.; heterocycle derivs. for inhibiting adenylate cyclase and methods of use for **treating** intestinal fluid loss and whooping cough and anthrax and conditions assocd. with smooth muscle contraction)
IT Prostaglandins
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(analogs; heterocycle derivs. for inhibiting adenylate cyclase and methods of use for **treating** intestinal fluid loss and whooping cough and anthrax and conditions assocd. with smooth muscle contraction)
IT Bacillus anthracis
(anthrax from; heterocycle derivs. for inhibiting adenylate cyclase and methods of use for **treating** intestinal fluid loss and whooping cough and anthrax and conditions assocd. with smooth muscle contraction)
IT Heterocyclic compounds
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(arom., di-Ph; heterocycle derivs. for inhibiting adenylate cyclase and methods of use for **treating** intestinal fluid loss and whooping cough and anthrax and conditions assocd. with smooth muscle contraction)
IT ADP ribosylation
(by pathogenic organisms; heterocycle derivs. for inhibiting adenylate

cyclase and methods of use for **treating** intestinal fluid loss and whooping cough and anthrax and conditions assocd. with smooth muscle contraction)

IT Toxins
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(cholera, intestinal fluid loss stimulation by; heterocycle derivs. for inhibiting adenylate cyclase and methods of use for **treating** intestinal fluid loss and whooping cough and anthrax and conditions assocd. with smooth muscle contraction)

IT Intestine, disease
(fluid loss; heterocycle derivs. for inhibiting adenylate cyclase and methods of use for **treating** intestinal fluid loss and whooping cough and anthrax and conditions assocd. with smooth muscle contraction)

IT Antidiarrheals
Pertussis
(heterocycle derivs. for inhibiting adenylate cyclase and methods of use for **treating** intestinal fluid loss and whooping cough and anthrax and conditions assocd. with smooth muscle contraction)

IT Heterocyclic compounds
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(heterocycle derivs. for inhibiting adenylate cyclase and methods of use for **treating** intestinal fluid loss and whooping cough and anthrax and conditions assocd. with smooth muscle contraction)

IT Aromatic compounds
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(heterocyclic, di-Ph; heterocycle derivs. for inhibiting adenylate cyclase and methods of use for **treating** intestinal fluid loss and whooping cough and anthrax and conditions assocd. with smooth muscle contraction)

IT Intestine, disease
(infection, fluid loss assocd. with pathogenic; heterocycle derivs. for inhibiting adenylate cyclase and methods of use for **treating** intestinal fluid loss and whooping cough and anthrax and conditions assocd. with smooth muscle contraction)

IT Pathogen
(intestinal fluid loss assocd. with; heterocycle derivs. for inhibiting adenylate cyclase and methods of use for **treating** intestinal fluid loss and whooping cough and anthrax and conditions assocd. with smooth muscle contraction)

IT Body fluid
(loss; heterocycle derivs. for inhibiting adenylate cyclase and methods of use for **treating** intestinal fluid loss and whooping cough and anthrax and conditions assocd. with smooth muscle contraction)

IT Muscle relaxants
(smooth; heterocycle derivs. for inhibiting adenylate cyclase and methods of use for **treating** intestinal fluid loss and whooping cough and anthrax and conditions assocd. with smooth muscle contraction)

IT 56-65-5, 5'-ATP, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(cAMP formation from; heterocycle derivs. for inhibiting adenylate cyclase and methods of use for **treating** intestinal fluid loss and whooping cough and anthrax and conditions assocd. with smooth muscle contraction)

IT 363-24-6, PGE2
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(cAMP formation stimulation by and reaction with L-histidine; heterocycle derivs. for inhibiting adenylate cyclase and methods of use for **treating** intestinal fluid loss and whooping cough and anthrax)

IT 60-92-4, CAMP
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(formation; heterocycle derivs. for inhibiting adenylate cyclase and methods of use for **treating** intestinal fluid loss and whooping cough and anthrax and conditions assocd. with smooth muscle contraction)
IT 9012-42-4, Adenylate cyclase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(heterocycle derivs. for inhibiting adenylate cyclase and methods of use for **treating** intestinal fluid loss and whooping cough and anthrax and conditions assocd. with smooth muscle contraction)
IT 380153-74-2 380153-75-3
RL: DMA (Drug mechanism of action); FMU (Formation, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); FORM (Formation, nonpreparative); USES (Uses)
(heterocycle derivs. for inhibiting adenylate cyclase and methods of use for **treating** intestinal fluid loss and whooping cough and anthrax and conditions assocd. with smooth muscle contraction)
IT 53-86-1, Indomethacin 71-00-1, L-Histidine, biological studies 288-32-4, Imidazole, biological studies 443-48-1, Metronidazole 88149-94-4 **162011-90-7 169590-42-5** 188817-13-2
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(heterocycle derivs. for inhibiting adenylate cyclase and methods of use for **treating** intestinal fluid loss and whooping cough and anthrax and conditions assocd. with smooth muscle contraction)

L200 ANSWER 29 OF 36 CAPLUS COPYRIGHT 2003 ACS
AN 2001:857055 CAPLUS
DN 136:194000
TI **Celecoxib**, a selective cyclo-oxygenase-2 inhibitor reduces the severity of experimental colitis induced by dinitrobenzene sulfonic acid in rats
AU Cuzzocrea, Salvatore; Mazzon, Emanuela; Serraino, Ivana; Dugo, Laura; Centorrino, Tommaso; Ciccolo, Antonio; Sautebin, Lidia; Caputi, Achille P.
CS Institute of Pharmacology, School of Medicine, University of Messina, Torre Biologica, Policlinico Universitario Via C. Valera, Gazzi, Messina, 98100, Italy
SO European Journal of Pharmacology (2001), 431(1), 91-102
CODEN: EJPHAZ; ISSN: 0014-2999
PB Elsevier Science B.V.
DT Journal
LA English
CC 1-9 (Pharmacology)
AB Inflammatory bowel disease is characterized by oxidative and nitrosative stress, leukocyte infiltration, upregulation of the expression of intercellular adhesion mol. 1 (ICAM-1) and upregulation of P-selectin in the colon. Here, we investigate the effects of the selective cyclo-oxygenase-2 inhibitor, **celecoxib**, in rats subjected to exptl. colitis. Colitis was induced in rats by intracolonic instillation of dinitrobenzene sulfonic acid (DNBS). Rats experienced hemorrhagic **diarrhea** and wt. loss. At 4 days after administration of DNBS, the mucosa of the colon exhibited large areas of necrosis. Neutrophil infiltration (detd. by histol., as well as an increase in myeloperoxidase activity in the mucosa) was assocd. with upregulation of ICAM-1 and P-selectin, as well as high tissue levels of malondialdehyde. Immunohistochem. for nitrotyrosine and poly(ADP-ribose) polymerase showed intense staining in the inflamed colon. **Celecoxib** (5 mg/kg twice a day orally) significantly reduced the degree of hemorrhagic **diarrhea** and the wt. loss caused by administration of DNBS. **Celecoxib** also caused a substantial redn. of (i) the degree of colonic injury, (ii) the rise in myeloperoxidase activity (mucosa), (iii) the increase in the tissue levels of malondialdehyde, (iv) the increase in staining (immunohistochem.) for nitrotyrosine, as well as (v) the

upregulation of ICAM-1 and P-selectin caused by DNBS in the colon. Thus, we provide the first evidence that a selective cyclo-oxygenase-2 inhibitor **celecoxib** reduces the degree of colitis caused by DNBS.

ST **celecoxib** colitis **treatment**

IT Cell adhesion molecules
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(ICAM-1 (intercellular adhesion mol. 1); **celecoxib**, a selective cyclo-oxygenase-2 inhibitor reduces the severity of exptl. colitis induced by dinitrobenzene sulfonic acid in rats)

IT Selectins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(P-; **celecoxib**, a selective cyclo-oxygenase-2 inhibitor reduces the severity of exptl. colitis induced by dinitrobenzene sulfonic acid in rats)

IT Oxidative stress, biological
(**celecoxib**, a selective cyclo-oxygenase-2 inhibitor reduces the severity of exptl. colitis induced by dinitrobenzene sulfonic acid in rats)

IT Intestine, disease
(colitis; **celecoxib**, a selective cyclo-oxygenase-2 inhibitor reduces the severity of exptl. colitis induced by dinitrobenzene sulfonic acid in rats)

IT Neutrophil
(infiltration; **celecoxib**, a selective cyclo-oxygenase-2 inhibitor reduces the severity of exptl. colitis induced by dinitrobenzene sulfonic acid in rats)

IT Stress, animal
(nitrosative; **celecoxib**, a selective cyclo-oxygenase-2 inhibitor reduces the severity of exptl. colitis induced by dinitrobenzene sulfonic acid in rats)

IT 9003-99-0, Myeloperoxidase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**celecoxib**, a selective cyclo-oxygenase-2 inhibitor reduces the severity of exptl. colitis induced by dinitrobenzene sulfonic acid in rats)

IT **169590-42-5, Celecoxib**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**celecoxib**, a selective cyclo-oxygenase-2 inhibitor reduces the severity of exptl. colitis induced by dinitrobenzene sulfonic acid in rats)

RE.CNT 60 THERE ARE 60 CITED REFERENCES AVAILABLE FOR THIS RECORD

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L200 ANSWER 30 OF 36 CAPLUS COPYRIGHT 2003 ACS
AN 2001:167798 CAPLUS
DN 134:202695
TI Method for **treating** or preventing chronic **prostatitis** or chronic pelvic pain syndrome with COX-2 selective inhibitor
IN Nickel, Curtis J.; Stoner, Elizabeth; Waldstreicher, Joanne; Pontari, Michel A.
PA Merck & Co., Inc., USA; Temple University - of the Commonwealth System of Higher Education
SO PCT Int. Appl., 13 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K031-18
CC 1-7 (Pharmacology)
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2001015687	A1	20010308	WO 2000-US23100	20000824

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD,

SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

US 6403640 B1 20020611 US 2000-644998 20000824
EP 1212051 A1 20020612 EP 2000-961351 20000824
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL

PRAI US 1999-151126P P 19990827
WO 2000-US23100 W 20000824

AB The use of a COX-2 selective inhibitor for the **treatment** or prevention of chronic **prostatitis** or chronic pelvic pain syndrome is disclosed.

ST COX2 inhibitor **prostatitis** chronic pelvic pain syndrome; cyclooxygenase 2 inhibitor **treatment** chronic **prostatitis**

IT Prostate-specific antigen
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(conjugates, in combination with COX-2 inhibitor; COX-2 selective inhibitor for **treatment** or prevention of chronic **prostatitis** or chronic pelvic pain syndrome)

IT Analgesics
Antibiotics
Cholinergic antagonists
(in combination with COX-2 inhibitor; COX-2 selective inhibitor for **treatment** or prevention of chronic **prostatitis** or chronic pelvic pain syndrome)

IT Body, anatomical
(pelvis, chronic pelvic pain syndrome; COX-2 selective inhibitor for **treatment** or prevention of chronic **prostatitis** or chronic pelvic pain syndrome)

IT Prostate gland
(**prostatitis**; COX-2 selective inhibitor for **treatment** or prevention of chronic **prostatitis** or chronic pelvic pain syndrome)

IT Drug delivery systems
(topical, urinary analgesics, in combination with COX-2 inhibitor; COX-2 selective inhibitor for **treatment** or prevention of chronic **prostatitis** or chronic pelvic pain syndrome)

IT Adrenoceptor antagonists
(.alpha.1-, in combination with COX-2 inhibitor; COX-2 selective inhibitor for **treatment** or prevention of chronic **prostatitis** or chronic pelvic pain syndrome)

IT 51803-78-2, Nimesulide 71125-38-7, Meloxicam 80937-31-1, Flosulide 88149-94-4, DuP 697 123653-11-2, NS 398 **162011-90-7**, **Rofecoxib** 162054-19-5, SC-58125 **169590-42-5**, **Celecoxib** 179382-91-3, RS 57067 181695-72-7, Valdecoxib 198470-84-7, Parecoxib 202409-33-4, MK-663
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(COX-2 selective inhibitor for **treatment** or prevention of chronic **prostatitis** or chronic pelvic pain syndrome)

IT 39391-18-9
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(cyclooxygenase-2, selective inhibitors; COX-2 selective inhibitor for **treatment** or prevention of chronic **prostatitis** or chronic pelvic pain syndrome)

IT 9081-34-9, 5.alpha.-Reductase
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors, in combination with COX-2 inhibitor; COX-2 selective inhibitor for **treatment** or prevention of chronic **prostatitis** or chronic pelvic pain syndrome)

RE.CNT 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
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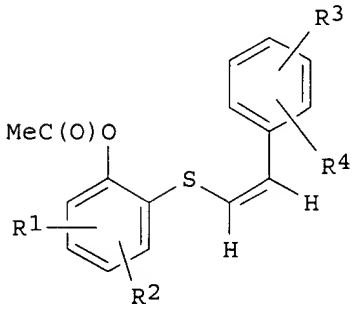
L200 ANSWER 31 OF 36 CAPLUS COPYRIGHT 2003 ACS
AN 2000:900773 CAPLUS
DN 134:41979
TI (Z)-Styryl acetoxyphenyl sulfides as cyclooxygenase inhibitors
IN Reddy, E. Premkumar; Reddy, M. V. Ramana
PA Temple University - of the Commonwealth System of Higher Education, USA
SO PCT Int. Appl., 28 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C12N
CC 25-18 (Benzene, Its Derivatives, and Condensed Benzenoid Compounds)
Section cross-reference(s): 1, 7, 35, 63
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000077169	A2	20001221	WO 2000-US16725	20000616
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	AU 2000056207	A5	20010102	AU 2000-56207	20000616
	EP 1191929	A2	20020403	EP 2000-941505	20000616
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
PRAI	US 1999-139445P	P	19990616		
	WO 2000-US16725	W	20000616		

OS MARPAT 134:41979
GI



I

AB (Z)-Styryl acetoxyphenyl sulfides (shown as I; R1, R2, R3, R4 = H, halogen, OH, C1-C8 alkyl, C1-C6 alkoxy, NO2, CN, OAc, amino, carboxy, sulfamyl, lower acylsulfamyl and trifluoromethyl), a method for their prepn., and their usefulness in **treating** inflammation and

cyclooxygenase-mediated disorders are claimed. The compds. of the invention preferably are characterized by a large selectivity ratio for cyclooxygenase-2 inhibition over cyclooxygenase-1 inhibition; data are reported for I (R1 = R2 = R3 = H; R4 = H, 4-F, 2-Cl, 4-Cl, 3-acetoxy). The claimed method of prepn. comprises reacting (Z)-styryl hydroxyphenyl sulfides with acetic anhydride. The (Z)-styryl hydroxyphenyl sulfides were made from sodium 2-hydroxybenzenethiolates and phenylacetylenes. I undergo radical polymn. to give polyolefins. (Z)-styryl acetoxyphenyl sulfide was significantly more effective than **Celecoxib** with respect to inhibition of colorectal cancer cell colony growth.

ST styryl acetoxyphenyl sulfide prepn inhibition cyclooxygenase 2 polymn; antiinflammatory cyclooxygenase 2 inhibition styryl acetoxyphenyl sulfide prepn; antitumor agent cyclooxygenase 2 inhibition styryl acetoxyphenyl sulfide prepn; angiogenesis inhibitor cyclooxygenase 2 inhibition styryl acetoxyphenyl sulfide prepn

IT Bronchi
(bronchitis; prepn. of styryl acetoxyphenyl sulfides useful as inhibitors of cyclooxygenase-2 for **treating**)

IT Digestive tract
(disease; prepn. of styryl acetoxyphenyl sulfides useful as inhibitors of cyclooxygenase-2 for **treating**)

IT Drug delivery systems
(of styryl acetoxyphenyl sulfides useful as selective inhibitors of cyclooxygenase-2)

IT Polyolefins
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. by radical polymn. of styryl acetoxyphenyl sulfides)

IT Antitumor agents
(prepn. of styryl acetoxyphenyl sulfides useful against neoplasias that produce prostaglandins)

IT Burn
Dermatitis
Psoriasis
(prepn. of styryl acetoxyphenyl sulfides useful as inhibitors of cyclooxygenase-2 for **treating**)

IT Analgesics
Angiogenesis inhibitors
Anti-inflammatory agents
Antiarthritics
Antiasthmatics
Antipyretics
Antiviral agents
(prepn. of styryl acetoxyphenyl sulfides useful as selective inhibitors of cyclooxygenase-2)

IT Thioethers
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of styryl acetoxyphenyl sulfides useful as selective inhibitors of cyclooxygenase-2)

IT Tendon
(tendinitis; prepn. of styryl acetoxyphenyl sulfides useful as inhibitors of cyclooxygenase-2 for **treating**)

IT 536-74-3, Phenylacetylene 766-96-1, 4-Bromophenylacetylene 766-97-2, 4-Methylphenylacetylene 766-98-3, 4-Fluorophenylacetylene 768-60-5, 4-Methoxyphenylacetylene 873-31-4, 2-Chlorophenylacetylene 873-73-4, 4-Chlorophenylacetylene 937-31-5, 4-Nitrophenylacetylene 10401-11-3, 3-Hydroxyphenylacetylene 40307-11-7, 4-Ethylphenylacetylene 79887-10-8, 4-Pentylphenylacetylene
RL: RCT (Reactant); RACT (Reactant or reagent)
(addn. reactions with 2-acetoxythiophenols in presence of sodium followed by condensation with acetic anhydride)

IT 313269-75-9, 2-Acetoxybenzenethiol
RL: RCT (Reactant); RACT (Reactant or reagent)

(addn. reactions with phenylacetylenes in presence of sodium)
IT 1121-24-0, 2-Hydroxythiophenol
RL: RCT (Reactant); RACT (Reactant or reagent)
(addn. reactions with phenylacetylenes in presence of sodium followed by condensation with acetic anhydride)
IT 39391-18-9
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(cyclooxygenase-2; prepn. of styryl acetoxyphenyl sulfides useful as selective inhibitors of cyclooxygenase-2 relative to cyclooxygenase-1)
IT 313269-63-5P, (Z)-Styryl 2-acetoxyphenyl sulfide 313269-64-6P, (Z)-4-Fluorostyryl 2-acetoxyphenyl sulfide 313269-65-7P, (Z)-2-Chlorostyryl 2-acetoxyphenyl sulfide 313269-66-8P, (Z)-4-Chlorostyryl 2-acetoxyphenyl sulfide 313269-72-6P, (Z)-3-Acetoxystyryl 2-acetoxyphenyl sulfide
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of styryl acetoxyphenyl sulfides useful as selective inhibitors of cyclooxygenase-2)
IT 313269-67-9P, (Z)-4-Bromostyryl 2-acetoxyphenyl sulfide 313269-68-0P, (Z)-4-Methylstyryl 2-acetoxyphenyl sulfide 313269-69-1P, (Z)-4-Ethylstyryl 2-acetoxyphenyl sulfide 313269-70-4P, (Z)-4-Pentylstyryl 2-acetoxyphenyl sulfide 313269-71-5P, (Z)-3-Hydroxystyryl 2-acetoxyphenyl sulfide 313269-73-7P, (Z)-4-Methoxystyryl 2-acetoxyphenyl sulfide 313269-74-8P, (Z)-4-Nitrostyryl 2-acetoxyphenyl sulfide
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of styryl acetoxyphenyl sulfides useful as selective inhibitors of cyclooxygenase-2)

L200 ANSWER 32 OF 36 CAPLUS COPYRIGHT 2003 ACS
AN 2000:757695 CAPLUS
DN 134:65940
TI Topical application of a selective cyclooxygenase inhibitor suppresses UVB mediated cutaneous inflammation
AU Wilgus, Traci A.; Ross, Mary S.; Parrett, Michelle L.; Oberyszyn, Tatiana M.
CS Department of Molecular Virology, Immunology and Medical Genetics, The College of Medicine, The Ohio State University, Columbus, OH, 43210, USA
SO Prostaglandins & Other Lipid Mediators (2000), 62(4), 367-384
CODEN: POLMFL; ISSN: 1098-8823
PB Elsevier Science Inc.
DT Journal
LA English
CC 1-7 (Pharmacology)
Section cross-reference(s): 8
AB This work compared the effects of topical **treatment** with **Celecoxib** (a specific COX [cyclooxygenase] 2 inhibitor) and ibuprofen (a nonspecific COX inhibitor) on the acute UVB-induced cutaneous inflammatory response in mice. The specific inhibition of COX-2 effectively reduced many parameters of UVB-mediated inflammation, including edema, dermal neutrophil infiltration and activation, plasma PGE2 levels and the formation of sunburn cells. By inhibiting this inflammatory response, topical **Celecoxib treatment** may ultimately be effective in preventing UVB-induced tumor development in the skin.
ST **skin inflammation** UV radiation **Celecoxib** cyclooxygenase inhibitor; antiinflammatory **Celecoxib** cyclooxygenase inhibitor skin UV radiation
IT Anti-inflammatory agents
Dermatitis
UV B radiation

(cyclooxygenase 2 inhibitor **Celecoxib** suppression of UVB-mediated cutaneous inflammation)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(for cyclooxygenase 2; cyclooxygenase 2 inhibitor **Celecoxib** suppression of UVB-mediated cutaneous inflammation)

IT **169590-42-5, Celecoxib**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cyclooxygenase 2 inhibitor **Celecoxib** suppression of UVB-mediated cutaneous inflammation)

IT 39391-18-9
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cyclooxygenase-2, inhibitors; cyclooxygenase 2 inhibitor **Celecoxib** suppression of UVB-mediated cutaneous inflammation)

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L200 ANSWER 33 OF 36 CAPLUS COPYRIGHT 2003 ACS
AN 2000:72484 CAPLUS
DN 132:87911
TI **Celecoxib** versus diclofenac in long-term management of rheumatoid arthritis: randomized double-blind comparison
AU Emery, Paul; Zeidler, Henning; Kvien, Tore K.; Guslandi, Mario; Naudin, Raphael; Stead, Helen; Verburg, Kenneth M.; Isakson, Peter C.; Hubbard, Richard C.; Geis, G. Steven
CS Department of Rheumatology and Rehabilltation, University of Leeds, Leeds, UK
SO Lancet (1999), 354(9196), 2106-2111
CODEN: LANCAO; ISSN: 0140-6736
PB Lancet Ltd.
DT Journal
LA English
CC 1-7 (Pharmacology)
AB Background: Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit cyclo-oxygenase (COX), which leads to suppression of COX-1-mediated prodn. of gastrointestinal-protective prostaglandins. Gastrointestinal injury is a common outcome. We compared the efficacy, safety, and tolerability of long-term therapy with **celecoxib**, a COX-1 sparing inhibitor of COX-2, with diclofenac, a non-specific COX inhibitor. Methods: 655 patients with adult-onset rheumatoid arthritis of at least 6 mo' duration

were randomly assigned oral **celecoxib** 200 mg twice daily or diclofenac SR 75 mg twice daily for 24 wk. Anti-inflammatory and analgesic activity and tolerability were assessed at baseline, every 4 wk, and at week 24. We assessed gastrointestinal safety by upper-gastrointestinal endoscopy within 7 days of the last **treatment** dose at centers where the procedure was available. Anal. was by intention-to-**treat**. Findings: 430 patients underwent endoscopy (**celecoxib** n=212, diclofenac n=218). The two drugs were similar in management of rheumatoid arthritis pain and inflammation. Gastroduodenal ulcers were detected endoscopically in 33 (15%) patients **treated** with diclofenac and in eight (4%) in the **celecoxib** group ($p<0.001$). The rate of withdrawal for any gastrointestinal-related adverse event, most commonly abdominal pain, **diarrhea**, and dyspepsia, was nearly three times higher in the diclofenac-**treated** group than in the **celecoxib** group (16 vs. 6%; $p<0.001$). Interpretation: **Celecoxib** showed sustained anti-inflammatory and analgesic activity similar to diclofenac, with a lower frequency of upper gastrointestinal ulceration or gastrointestinal adverse events, and tolerability was better.

ST **celecoxib** diclofenac rheumatoid arthritis stomach ulcer

IT Antirheumatic agents
Dyspepsia
Ulcer
(efficacy and safety of **celecoxib** vs. diclofenac in long-term management of rheumatoid arthritis in humans)

IT 15307-86-5, Diclofenac **169590-42-5**, **Celecoxib**
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(efficacy and safety of **celecoxib** vs. diclofenac in long-term management of rheumatoid arthritis in humans)

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L200 ANSWER 34 OF 36 CAPLUS COPYRIGHT 2003 ACS
AN 1999:669180 CAPLUS
DN 132:160652
TI **Celecoxib**, a selective cyclooxygenase-2 inhibitor for the **treatment** of rheumatoid arthritis and osteoarthritis
AU Goldenberg, Marvin M.
CS Mount Sinai NYU Health, New York, NY, USA
SO Clinical Therapeutics (1999), 21(9), 1497-1513
CODEN: CLTHDG; ISSN: 0149-2918
PB Excerpta Medica
DT Journal; General Review
LA English
CC 1-0 (Pharmacology)
AB A review with 56 refs. Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most frequently prescribed drugs, despite their well-established assocn. with gastroduodenal injury. Recent discovery of the cyclooxygenase (COX) isoenzymes COX-1 and COX-2 has improved our knowledge of the action of NSAIDs. COX-1 is continuously expressed in almost all tissues, where it converts arachidonate to the prostaglandins (PGs) important in homeostatic function; COX-2 is present in immune cells, blood vessel endothelial cells, and synovial fibroblasts. Classic NSAIDs inhibit both COX isoenzymes by occupying the cyclooxygenase-active site, preventing access by arachidonic acid. In theory, a drug such as **celecoxib** that selectively inhibited COX-2 might block inflammation, pain, and fever while reducing the side effects (gastric erosions and ulcers) assocd. with inhibition of COX-1. In animal models of inflammation and pain, **celecoxib** has shown marked suppression of PG prodn. and inflammation compared with indomethacin, the std. COX-1/COX-2 inhibitor. In clin. trials, **celecoxib** dosed at 100, 200, and 400 mg BID was found to significantly reduce the signs and symptoms of rheumatoid arthritis (RA) and osteoarthritis. In one RA study, **celecoxib** was found to be as clin. effective as diclofenac after 24 wk of **treatment**; at the end of the study, gastroduodenal ulcers occurred significantly more frequently in the diclofenac group (15%) than in the **celecoxib** group (4%). In a 1-wk endoscopy study comparing **celecoxib** with naproxen and placebo, the incidence of gastric erosions/ulcers was significantly greater in the naproxen group than in the **celecoxib** or placebo group. The most common adverse effects of **celecoxib** in clin. studies were headache, **diarrhea**, abdominal discomfort, and dizziness. **Celecoxib** has shown significant equiv. anti-inflammatory and analgesic efficacy and has produced less endoscopically apparent gastrointestinal (GI) ulceration or erosion than have 3 classic NSAIDs. Whether it will have long-term GI adverse effects or interact with other medications to cause serious adverse responses (eg, increased GI bleeding or rash in conjunction with other sulfonamide-like drugs) is unknown and remains to be established.
ST review COX2 inhibitor **celecoxib** rheumatoid arthritis osteoarthritis
IT Analgesics
Antiarthritics
Antirheumatic agents
(COX-2 inhibitor **celecoxib** for rheumatoid arthritis and osteoarthritis **treatment**)
IT Prostaglandins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(COX-2 inhibitor **celecoxib** for rheumatoid arthritis and osteoarthritis **treatment**)
IT Anti-inflammatory agents
(nonsteroidal; COX-2 inhibitor **celecoxib** for rheumatoid

arthritis and osteoarthritis **treatment**)
IT Digestive tract
(toxicity; COX-2 inhibitor **celecoxib** for rheumatoid arthritis and osteoarthritis **treatment**)
IT Stomach, disease
(ulcer; COX-2 inhibitor **celecoxib** for rheumatoid arthritis and osteoarthritis **treatment**)
IT **169590-42-5, Celecoxib**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(COX-2 inhibitor **celecoxib** for rheumatoid arthritis and osteoarthritis **treatment**)
IT 39391-18-9, Cyclooxygenase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(COX-2 inhibitor **celecoxib** for rheumatoid arthritis and osteoarthritis **treatment**)
RE.CNT 56 THERE ARE 56 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE

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L200 ANSWER 35 OF 36 CAPLUS COPYRIGHT 2003 ACS
AN 1997:562995 CAPLUS
DN 127:225303
TI Immunosuppressive combinations containing a cyclooxygenase-2 inhibitor and a leukotriene A4 hydrolase inhibitor
IN Gregory, Susan A.; Isakson, Peter C.; Anderson, Gary
PA G.D. Searle & Co., USA; Gregory, Susan A.; Isakson, Peter C.; Anderson, Gary
SO PCT Int. Appl., 77 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K045-06
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 28
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9729774	A1	19970821	WO 1997-US1421	19970211
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	CA 2246336	AA	19970821	CA 1997-2246336	19970211
	AU 9719525	A1	19970902	AU 1997-19525	19970211
	EP 880363	A1	19981202	EP 1997-907545	19970211
	EP 880363	B1	20020911		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
	JP 2001506574	T2	20010522	JP 1997-529358	19970211
	AT 223732	E	20020915	AT 1997-907545	19970211
	ES 2183140	T3	20030316	ES 1997-907545	19970211
	US 6407140	B1	20020618	US 2000-489311	20000121
	US 2003004191	A1	20030102	US 2002-137231	20020502
PRAI	US 1996-600655	A1	19960213		
	WO 1997-US1421	W	19970211		
	US 2000-489311	A3	20000121		

OS MARPAT 127:225303
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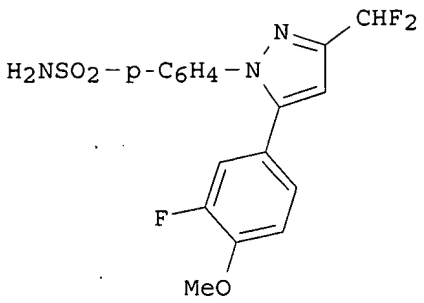

I

AB Immunosuppressant compns. contg. a combination of a cyclooxygenase-2 inhibitor (which inhibits conversion of arachidonic acid to prostaglandins) and a LTA4 hydrolase inhibitor are useful in reducing recipient rejection of transplanted organs and for **treatment** of autoimmune diseases. Thus, F2CHCO2Et reacted with 3-fluoro-4-methoxyacetophenone to form 4,4-difluoro-1-(3-fluoro-4-methoxyphenyl)butane-1,3-dione, which was condensed with 4-sulfonamidophenylhydrazine-HCl to produce the cyclooxygenase-2 inhibitor I. A formulation was prepd. contg. 350 mg I and 700 mg 3-[N-methyl-N-[3-[(4-phenylmethyl)phenoxy]propyl]amino]propanoic acid (LTA4 hydrolase inhibitor).

ST immunosuppressant cyclooxygenase inhibitor; leukotriene hydrolase inhibitor transplant rejection

IT Kidney, disease
(Goodpasture's syndrome; immunosuppressive combinations contg. cyclooxygenase-2 inhibitor and LTA4 hydrolase inhibitor)

IT Thyroid gland, disease
(autoimmune thyroiditis; immunosuppressive combinations contg. cyclooxygenase-2 inhibitor and LTA4 hydrolase inhibitor)

IT **Dermatitis**
(contact; immunosuppressive combinations contg. cyclooxygenase-2 inhibitor and LTA4 hydrolase inhibitor)

IT Allergy inhibitors
Allergy inhibitors
(delayed hypersensitivity; immunosuppressive combinations contg. cyclooxygenase-2 inhibitor and LTA4 hydrolase inhibitor)

IT Respiratory tract
(disease, hypersensitivity; immunosuppressive combinations contg. cyclooxygenase-2 inhibitor and LTA4 hydrolase inhibitor)

IT Kidney, disease
(glomerulonephritis; immunosuppressive combinations contg. cyclooxygenase-2 inhibitor and LTA4 hydrolase inhibitor)

IT Transplant and Transplantation
(graft-vs.-host reaction; immunosuppressive combinations contg. cyclooxygenase-2 inhibitor and LTA4 hydrolase inhibitor)

IT Anemia (disease)
(hemolytic, autoimmune; immunosuppressive combinations contg. cyclooxygenase-2 inhibitor and LTA4 hydrolase inhibitor)

IT Allergy
(hypersensitivity, respiratory tract; immunosuppressive combinations contg. cyclooxygenase-2 inhibitor and LTA4 hydrolase inhibitor)

IT Addison's disease
(idiopathic; immunosuppressive combinations contg. cyclooxygenase-2 inhibitor and LTA4 hydrolase inhibitor)

IT Allergy
(immediate hypersensitivity; immunosuppressive combinations contg. cyclooxygenase-2 inhibitor and LTA4 hydrolase inhibitor)

IT Allergy inhibitors
Anti-inflammatory agents
Antiasthmatics

Autoimmune disease
Encephalomyelitis
Graves' disease
Immunosuppressants
Meningitis
Myasthenia gravis
Sjogren's syndrome
Transplant rejection
Urticaria
(immunosuppressive combinations contg. cyclooxygenase-2 inhibitor and LTA4 hydrolase inhibitor)

IT Granuloma
(inhibitors; immunosuppressive combinations contg. cyclooxygenase-2 inhibitor and LTA4 hydrolase inhibitor)

IT Connective tissue
(mixed connective tissue disease; immunosuppressive combinations contg. cyclooxygenase-2 inhibitor and LTA4 hydrolase inhibitor)

IT Lung, disease
(pneumonitis, hypersensitive; immunosuppressive combinations contg. cyclooxygenase-2 inhibitor and LTA4 hydrolase inhibitor)

IT Shock (circulatory collapse)
(septic; immunosuppressive combinations contg. cyclooxygenase-2 inhibitor and LTA4 hydrolase inhibitor)

IT Platelet (blood)
(thrombocytopenia; immunosuppressive combinations contg. cyclooxygenase-2 inhibitor and LTA4 hydrolase inhibitor)

IT Purpura (disease)
(thrombocytopenic, autoimmune; immunosuppressive combinations contg. cyclooxygenase-2 inhibitor and LTA4 hydrolase inhibitor)

IT Thyroid gland, disease
Thyroid gland, disease
(thyroiditis; immunosuppressive combinations contg. cyclooxygenase-2 inhibitor and LTA4 hydrolase inhibitor)

IT 39391-18-9
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(2, inhibitors; immunosuppressive combinations contg. cyclooxygenase-2 inhibitor and LTA4 hydrolase inhibitor)

IT 142259-95-8, RP-64966 179021-09-1 179021-10-4 179022-08-3
186901-93-9 186901-94-0 186901-95-1 186901-96-2 186901-97-3
186901-98-4 194997-63-2
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(LTA4 hydrolase inhibitor; immunosuppressive combinations contg. cyclooxygenase-2 inhibitor and LTA4 hydrolase inhibitor)

IT 71125-38-7, Meloxicam 80937-31-1, Flosulide 88149-94-4, DuP 697
123653-11-2, NS-398 162011-83-8 169590-41-4 **169590-42-5**
170569-86-5 177660-77-4 177660-80-9 177660-88-7 181695-76-1
185344-61-0 194997-65-4 194997-66-5 194997-67-6
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cyclooxygenase-2 inhibitor; immunosuppressive combinations contg. cyclooxygenase-2 inhibitor and LTA4 hydrolase inhibitor)

IT **162011-90-7**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(immunosuppressive combinations contg. cyclooxygenase-2 inhibitor and LTA4 hydrolase inhibitor)

IT 99-91-2 321-28-8, 2-Fluoroanisole 383-63-1, Ethyl trifluoroacetate
454-31-9, Ethyl difluoroacetate 27918-19-0, 4-Sulfonamidophenylhydrazine hydrochloride
RL: RCT (Reactant); RACT (Reactant or reagent)

(immunosuppressive combinations contg. cyclooxygenase-2 inhibitor and LTA4 hydrolase inhibitor)

IT 455-91-4P 18931-60-7P 170570-77-1P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(immunosuppressive combinations contg. cyclooxygenase-2 inhibitor and LTA4 hydrolase inhibitor)

IT 90119-07-6, Leukotriene A4 hydrolase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; immunosuppressive combinations contg. cyclooxygenase-2 inhibitor and LTA4 hydrolase inhibitor)

L200 ANSWER 36 OF 36 CAPLUS COPYRIGHT 2003 ACS
AN 1997:557660 CAPLUS
DN 127:239120
TI Compositions comprising a cyclooxygenase-2 inhibitor and a leukotriene B4 receptor antagonist for reducing transplant rejection
IN Gregory, Susan A.; Isakson, Peter C.; Anderson, Gary
PA G.D. Searle & Co., USA; Gregory, Susan A.; Isakson, Peter C.; Anderson, Gary
SO PCT Int. Appl., 63 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K045-06
ICS A61K031-00; A61K031-10; A61K031-18; A61K038-13
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1, 2
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9729775	A1	19970821	WO 1997-US1422	19970211
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	CA 2246356	AA	19970821	CA 1997-2246356	19970211
	AU 9722500	A1	19970902	AU 1997-22500	19970211
	EP 880362	A1	19981202	EP 1997-905663	19970211
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
	JP 2000505445	T2	20000509	JP 1997-529359	19970211
	US 6172096	B1	20010109	US 1998-75633	19980511
PRAI	US 1996-600580	A1	19960213		
	WO 1997-US1422	W	19970211		

OS MARPAT 127:239120
AB **Treatment** with a cyclooxygenase-2 inhibitor and a leukotriene B4 receptor antagonist is described as being useful in reducing recipient rejection of transplanted organs and for **treatment** of autoimmune diseases.
ST immunodepressant transplant cyclooxygenase2 inhibitor leukotrieneB4 antagonist
IT Kidney, disease
(Goodpasture's syndrome; compns. comprising a cyclooxygenase-2 inhibitor and a leukotriene B4 receptor antagonist for reducing transplant rejection)
IT Leukocyte
(activation of, inhibitors of; compns. comprising a cyclooxygenase-2 inhibitor and a leukotriene B4 receptor antagonist for reducing transplant rejection)
IT Anti-inflammatory agents

Autoimmune disease
Encephalomyelitis
Granuloma
Immunosuppressants
Meningitis
Urticaria
(compns. comprising a cyclooxygenase-2 inhibitor and a leukotriene B4 receptor antagonist for reducing transplant rejection)

IT Myasthenia gravis
Sjogren's syndrome
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(compns. comprising a cyclooxygenase-2 inhibitor and a leukotriene B4 receptor antagonist for reducing transplant rejection)

IT **Dermatitis**
(contact; compns. comprising a cyclooxygenase-2 inhibitor and a leukotriene B4 receptor antagonist for reducing transplant rejection)

IT Drug delivery systems
(emulsions; compns. comprising a cyclooxygenase-2 inhibitor and a leukotriene B4 receptor antagonist for reducing transplant rejection)

IT Kidney, disease
(glomerulonephritis; compns. comprising a cyclooxygenase-2 inhibitor and a leukotriene B4 receptor antagonist for reducing transplant rejection)

IT Transplant and Transplantation
(graft-vs.-host reaction; compns. comprising a cyclooxygenase-2 inhibitor and a leukotriene B4 receptor antagonist for reducing transplant rejection)

IT Anemia (disease)
(hemolytic; compns. comprising a cyclooxygenase-2 inhibitor and a leukotriene B4 receptor antagonist for reducing transplant rejection)

IT Lung, disease
(hypersensitivity pneumonitis; compns. comprising a cyclooxygenase-2 inhibitor and a leukotriene B4 receptor antagonist for reducing transplant rejection)

IT Addison's disease
(idiopathic; compns. comprising a cyclooxygenase-2 inhibitor and a leukotriene B4 receptor antagonist for reducing transplant rejection)

IT Leukotriene receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(leukotriene B4, antagonists; compns. comprising a cyclooxygenase-2 inhibitor and a leukotriene B4 receptor antagonist for reducing transplant rejection)

IT Drug delivery systems
(oral; compns. comprising a cyclooxygenase-2 inhibitor and a leukotriene B4 receptor antagonist for reducing transplant rejection)

IT Shock (circulatory collapse)
(septic; compns. comprising a cyclooxygenase-2 inhibitor and a leukotriene B4 receptor antagonist for reducing transplant rejection)

IT Purpura (disease)
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(thrombocytopenic, autoimmune; compns. comprising a cyclooxygenase-2 inhibitor and a leukotriene B4 receptor antagonist for reducing transplant rejection)

IT Thyroid gland, disease
Thyroid gland, disease
(thyroiditis; compns. comprising a cyclooxygenase-2 inhibitor and a leukotriene B4 receptor antagonist for reducing transplant rejection)

IT 39391-18-9
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(2, antagonists; compns. comprising a cyclooxygenase-2 inhibitor and a

leukotriene B4 receptor antagonist for reducing transplant rejection)

IT 127378-46-5, CI 987
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(CI 987; compns. comprising a cyclooxygenase-2 inhibitor and a leukotriene B4 receptor antagonist for reducing transplant rejection)

IT 170569-86-5P 195061-35-9P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(compns. comprising a cyclooxygenase-2 inhibitor and a leukotriene B4 receptor antagonist for reducing transplant rejection)

IT 32222-06-3, Calcitriol 59865-13-3, Cyclosporin a 60940-34-3, Ebselen 71125-38-7, Meloxicam 79217-60-0, Cyclosporin 80937-31-1, Flosulide 85259-71-8, BAY 0-8276 88149-94-4, Dup 697 93014-16-5 101910-24-1, PF-5901 110501-66-1, TMK-688 111908-95-3, SK&F-104493 117423-74-2, LY 223982 117423-95-7, LY 213024 117690-79-6, LY-255283 118414-82-7, MK-886 119261-58-4, TEI 1338 120072-59-5, SC-41930 123653-11-2, NS-398 128253-31-6, Bay-x-1005 130211-75-5, T-757 132734-43-1, LY 233569 133430-69-0, ETH-615 134578-96-4, ONO LB457 135199-82-5, LY 264086 135893-33-3, PF 10042 136326-31-3, WAY 121006 141059-52-1, SC-51146 141748-00-7, RP 69698 141835-49-6, RG 14893 142422-79-5, RP 66153 146461-98-5, SM 15178 147030-01-1, MK-591 147398-01-4, CGS-25019C 147432-77-7, Ontazolast 150399-22-7, SB-201993 153034-77-6, LY 292728 153633-01-3, SC-53228 154413-61-3, SB-209247 158081-99-3, Pfizer 105696 161172-51-6, LY-293111 162011-83-8 **162011-90-7** 162153-46-0, SC 52798 169590-41-4 **169590-42-5** 177660-77-4 177660-80-9 177660-92-3 180208-37-1, SB-201146 181695-72-7 185344-51-8 185344-55-2 186912-85-6, ONO-LB-448 186912-92-5, RP 66364 186912-94-7, SC-50505 195061-34-8 195215-25-9, BPC 15 195215-47-5, MNX 160 195215-53-3, S 2474 195215-55-5, SR 2566
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(compns. comprising a cyclooxygenase-2 inhibitor and a leukotriene B4 receptor antagonist for reducing transplant rejection)

IT 99-91-2, 4'-Chloroacetophenone 383-63-1, Ethyl trifluoroacetate 454-31-9, Ethyl difluoroacetate 27918-19-0, 4-Sulfonamidophenyl hydrazine hydrochloride
RL: RCT (Reactant); RACT (Reactant or reagent)
(compns. comprising a cyclooxygenase-2 inhibitor and a leukotriene B4 receptor antagonist for reducing transplant rejection)

IT 455-91-4P, 3'-Fluoro-4'-methoxyacetophenone 18931-60-7P 170570-77-1P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(compns. comprising a cyclooxygenase-2 inhibitor and a leukotriene B4 receptor antagonist for reducing transplant rejection)

L200 ANSWER 5 OF 36 USPATFULL

AB The present invention provides methods for **treating** intestinal fluid loss, whooping cough, anthrax, and conditions associated with smooth muscle contraction. The present invention also provides methods for inhibiting adenylate cyclase in vivo and in vitro.

SUMM [0003] Diarrheal diseases in humans and non-human animals can be caused by several types of pathogens, including viruses, bacteria, parasites, and rotaviruses. The most prevalent are the bacteria Escherichia coli and Vibrio cholerea. Diarrheal diseases are a prevalent cause of morbidity and mortality in less developed countries. These diseases also afflict populations in developed countries. For example, each year in the US over 200,000 children 5 years and younger are hospitalized with acute diarrheal diseases. The infectious **diarrheas** are the leading cause of morbidity and mortality worldwide a common class of illness in the United States.

SUMM [0004] Due to its many causes, acute infectious **diarrhea** can occur more than once in the same person, and, therefore, it is unlike most chronic conditions which typically occur once. Unlike other digestive diseases, infectious **diarrheas** are communicable via person-to-person contact or through contaminated food or water and can spread endemically or in epidemics through households, schools, day-care centers, nursing homes, and communities. Diarrheal diseases also pose a serious challenge in the raising of non-human animals in the farming industry, particularly with young calves and pigs.

SUMM [0005] The present invention represents an advance in the art of **treating** intestinal fluid loss in a subject. The invention provides methods for **treating** intestinal fluid loss in a subject. The method includes administering to a subject who has or is at risk of developing intestinal fluid loss a composition that includes an effective amount of heterocycle-containing compounds such as a heterocycle derivative, for instance a diphenyl heterocycle derivative, a prostaglandin analog, or a combination thereof. In some embodiments of this aspect of the invention the fluid loss is not associated with a pathogen polypeptide having ADP-ribosylation activity, and in other aspects the intestinal fluid loss is associated with a pathogen polypeptide having ADP-ribosylation activity.

SUMM [0008] The present invention further provides a method for **treating** whooping cough in a subject, including administering to a subject who has or is at risk of developing whooping cough a composition that includes an effective amount of a heterocycle-containing compound.

SUMM [0009] The present invention also provides a method for **treating** anthrax in a subject, including administering to a subject who has or is at risk of developing anthrax a composition that includes an effective amount of a heterocycle-containing compound.

DRWD [0021] FIG. 11. **Celecoxib** reduced CT-induced fluid accumulation in murine intestinal loops. CT, cholera toxin; CT + **celecoxib** in loop, mice challenged with cholera toxin and two 80 microgram (mg) doses of **celecoxib** (one injected into the intestinal lumen at the time of challenge with CT, the second injected intraperitoneally two hours later); CT +**celecoxib** IP only, mice challenged with cholera toxin and two 80 microgram (.mu.g) doses of **celecoxib** (one injected intraperitoneally at the time of challenge with CT, the second injected intraperitoneally two hours later). The vertical bars indicate one standard error above or below the mean. The asterisks indicate a significant difference from the positive control group as determined by the Tukey test ($P<0.05$).

DRWD [0022] FIG. 12. Effect of imidazole (2.7 mmoles), PGE.sub.2-Histidine

adduct (52 .mu.moles) and **celecoxib** (0.52 mmoles) on the enzyme Adenylate Cyclase (4.6 nmoles). Blank has no enzyme and inhibitors, while Enzyme (E) has only enzyme and no inhibitors. Enzyme containing specific inhibitors are represented as E+imidazole, E+PGE.sub.2-Histidine and E+**celecoxib**. Significant difference from the control value (E) is indicated by *P.ltoreq.0.05 and *P.ltoreq.0.001 as determined by Student's t-test.

DRWD [0023] FIG. 13. Fluid accumulation in Cholera toxin challenged murine intestinal ligated loops **treated** with the COX-1 inhibitor SC-560. n, number of animals; CT 1 .mu.g/loop, 1 microgram of cholera toxin added to each loop; CT +9 nM SC-560, 1 microgram of cholera toxin and 9 nanomolar SC-560 added to each loop The asterisks indicate a significant difference from the positive control (CT) as determined by the Tukey test.

DRWD [0025] FIG. 15. IC.sub.50 of **celecoxib** for adenylate cyclase.

DETD [0039] **rofecoxib** (available under the trade designation **VIOXX**, from Merck & Co., Whitehouse Station, N.Y.), which has the following structure: ##STR9##

DETD [0040] **celecoxib** (available under the trade designation **CELEBREX**, from Searle and Co., Skokie, Ill.), which has the following structure: ##STR10##

DETD [0049] Typically, the compositions of the invention will be administered from about 1 to about 5 times per day. The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the subject **treated** and the particular mode of administration. A typical preparation will contain from about 5% to about 95% active compound (w/w). Preferably, such preparations contain from about 20% to about 80% active compound. The amount of heterocycle-containing compound in such therapeutically useful compositions is such that the dosage level will be effective to prevent or suppress the condition the subject has or is at risk for.

DETD [0055] The present invention is further directed to methods for **treating** certain conditions in a subject as well as various in vitro methods. The conditions include, for instance, intestinal fluid loss, whooping cough, anthrax, and smooth muscle contraction, and are described in greater detail herein. The methods include administering a composition including a heterocycle-containing compound to a subject who is at risk of developing or has developed one of the conditions. As used herein, the term "subject" includes humans, agriculturally important animals such as cows, pigs, poultry, sheep, and horses, as well as other animals (for instance, mice, rats, dogs, cats, and rabbits) that can be used as animal models in the study of the conditions described herein.

DETD [0056] **Treatment** of the conditions described herein can be prophylactic or, alternatively, can be initiated after the development of a condition described herein. **Treatment** that is prophylactic, for instance, initiated before a subject manifests symptoms of a condition described herein and/or before exposure to a pathogen associated with (i.e., caused by) one of the conditions described herein, is referred to herein as **treatment** of a subject that is "at risk" of developing the condition. Accordingly, administration of a composition can be performed before, during, or after the occurrence of the conditions described herein. **Treatment** initiated after the development of a condition may result in decreasing the severity of the symptoms of one of the conditions, or completely removing the symptoms. Non-limiting examples of subjects particularly suited to receiving the composition are those undergoing antibiotic **treatment**, in particular the elderly and the very young, preferably antibiotic **treatment** that has been associated with antibiotic-associated colitis, those traveling to a location where pathogens causing intestinal fluid loss are endemic (for instance, those likely to contract Traveler's **diarrhea**), and those infected with HIV.

DETD [0057] A composition that is administered to a subject who has or is at risk of developing a condition described herein includes an effective

amount of a heterocycle-containing compound, preferably, a heterocycle derivative, and for certain embodiments, a diphenyl-substituted heterocycle derivative and/or a prostaglandin analog. As used herein, an "effective amount" is an amount effective to decrease or prevent (for prophylactic **treatment**) in a subject the symptoms associated with a condition described herein.

DETD [0058] An aspect of the invention is directed to a method of **treating** intestinal fluid loss in a subject. As used herein, the term "intestinal fluid loss" refers to various types of **diarrheas** (i.e., an increased frequency and/or liquidity of fecal discharges when compared to normal individuals with formed stools). Intestinal fluid loss can result from, for instance, increased fluid secretion (e.g., water and/or electrolytes) from intestinal cells into the intestinal lumen, decreased absorption of water and/or electrolytes from the intestinal lumen, and/or movement of blood and mucus into the intestinal lumen. Intestinal fluid loss is usually associated with the presence of a pathogen, although foods having hyperosmolality can elicit hypersecretion of water and electrolytes. This is in contrast to idiopathic inflammatory bowel disease, which includes Crohn's disease and ulcerative colitis. The latter chronic diseases are not associated with any particular infectious agent and result from uncontrolled inflammation of the colon and other regions of the intestinal tract.

DETD [0059] Pathogens that cause intestinal fluid loss include pathogens that are present in the intestinal lumen (for instance, Vibrio cholerae) or present in intestinal cells (for instance, Shigella), and pathogens that may not be present in the intestinal lumen or in intestinal cells (for instance, HIV). Examples of pathogens include viruses, parasites, and bacteria (see, for instance, Cotran et al., Robbins Pathologic Basis of Disease, 5.sup.th ed., W.B. Sanders Co., Philadelphia, pp. 328-335 (1994)). Intestinal fluid loss caused by pathogens is referred to in the art in numerous ways, including, for instance, **diarrhea**, dysentery, Travelers' **diarrhea**, and scours (in calves).

DETD [0066] In some aspects of the invention, when the intestinal fluid loss is not associated with a pathogen polypeptide having ADP-ribosylation activity (e.g., the intestinal fluid loss is associated with antibiotic **treatment**, the age of the subject, and/or infection by, for instance, a virus, a bacterium, a parasite, or a combination thereof), the heterocycle-containing compound present in the composition is a diphenyl heterocycle derivative, a prostaglandin analog, or a combination thereof. Examples of diphenyl heterocycles that can be used in this aspect of the invention include **celecoxib**, **rofecoxib**, SC-560, and DuP-697. Examples of prostaglandin analogs that can be used in this aspect of the invention include PGE.sub.2-histidine and PGE.sub.2-imidazole. Optionally, the composition can include, in addition to these heterocycle derivatives, an effective amount of metronidazole (available under the trade designation FLAGYL, from Searle and Co.) and/or an effective amount of indomethacin (available under the trade designation INDOCIN, from Merck & Co.). Of these two, metronidazole is preferred.

DETD [0067] In another aspect of the invention, when the intestinal fluid loss is associated with a pathogen polypeptide having ADP-ribosylation activity (e.g., the intestinal fluid loss is associated with V. cholerae, ETEC, or a combination thereof), the heterocycle-containing compound present in the composition is preferably an unsubstituted heterocyclic compound (e.g., imidazole), a diphenyl heterocycle derivative, a prostaglandin analog, or a combination thereof. More preferably, the heterocycle-containing compound present in the composition can be an unsubstituted heterocyclic compound (e.g., imidazole), a diphenyl heterocycle derivative, or a combination thereof. Examples of diphenyl heterocycles that can be used in this aspect of the invention include **rofecoxib**, SC-560, DuP-697, and in some embodiments, **celecoxib**. Preferably, the compositions do not include **celecoxib** for this method. Examples of a prostaglandin

analog that can be used in some embodiments of this aspect of the invention include PGE.sub.2-imidazole and PGE.sub.2-histidine. Compositions useful in this method can include an effective amount of metronidazole and/or an effective amount of indomethacin. Of these two, metronidazole is preferred.

DETD [0068] The invention is further directed to a method of **treating** whooping cough in a subject. Whooping cough is a disease of the respiratory tract caused by Bordetella pertussis. After exposure to B. pertussis, cells of the respiratory tract have increased cAMP levels. The method includes administering to a subject who has or is at risk of developing whooping cough a composition that includes an effective amount of a heterocycle-containing compound. The heterocycle-containing compound present in the composition is preferably an unsubstituted heterocyclic compound (e.g., imidazole), a diphenyl heterocycle derivative, a prostaglandin analog, or a combination thereof. The heterocycle-containing compound present in the composition is more preferably a diphenyl heterocycle derivative, a prostaglandin analog, or a combination thereof. Optionally, the composition can include, in addition to, these preferred heterocycle derivatives, an effective amount of metronidazole and/or indomethacin. Of these two, metronidazole is preferred.

DETD [0069] Another aspect of the invention is directed to a method for **treating** anthrax in a subject. Anthrax is an often fatal disease caused by Bacillus anthracis. One factor expressed by B. anthracis that is important in causing disease is edema factor, an adenylate cyclase which causes tissue edema by increasing cAMP levels. The method includes administering to a subject who has or is at risk of developing anthrax a composition comprising an effective amount of a heterocycle-containing compound. The heterocycle-containing compound present in the composition is preferably an unsubstituted heterocyclic compound (e.g., imidazole), a diphenyl heterocycle derivative, a prostaglandin analog, or a combination thereof. The heterocycle-containing compound present in the composition is more preferably a diphenyl heterocycle derivative, a prostaglandin analog, or a combination thereof. The heterocycle-containing compound present in the composition is more preferably a diphenyl heterocycle derivative, a prostaglandin analog, or a combination thereof. Optionally, the composition can include, in addition to, these preferred heterocycle derivatives, an effective amount of metronidazole and/or indomethacin. Of these two, metronidazole is preferred.

DETD [0072] The method for inhibiting adenylate cyclase in vivo includes contacting a cell that has been removed from a subject or is in a subject with a composition that includes an amount of a heterocycle derivative effective to inhibit the generation of cAMP from ATP. The cell includes adenylate cyclase and a pathogen polypeptide having ADP-ribosylation activity. Several conditions are associated with excessive adenylate cyclase activity and include, for instance, intestinal fluid loss as in diarrheal disease, tracheal and bronchial edema as in whooping cough, and pulmonary, gastrointestinal, and disseminated edema as in anthrax. Such conditions are described herein. The methods to inhibit adenylate cyclase can be used to **treat** such conditions.

DETD [0075] For methods of inhibiting adenylate cyclase, the heterocycle-containing compound present in the composition is preferably an unsubstituted heterocyclic compound (e.g., imidazole), a diphenyl heterocycle derivative, a prostaglandin analog, or a combination thereof. More preferably, the heterocycle-containing compound present in the composition can be an unsubstituted heterocyclic compound (e.g., imidazole), a diphenyl heterocycle derivative, or a combination thereof. Examples of diphenyl heterocycles that can be used in this aspect of the invention include **rofecoxib**, SC-560, DuP-697, and in some embodiments, **celecoxib**. Preferably, methods for inhibiting adenylate cyclase include **celecoxib** and DuP-697. Compositions useful in this method can include an effective amount of metronidazole

SUMM There are drugs that can be helpful in controlling Crohn's disease, but at present there is no cure. **Treatment** is aimed at correcting nutritional deficiencies, controlling inflammation, relieving the symptoms of abdominal pain, **diarrhea**, and **rectal bleeding**. Drugs known to be used for this condition can help, but side effects can be deleterious. Surgeries that may be performed to alleviate symptoms include the removal of inflamed areas, draining of abscesses, and bowel resection.

SUMM Mycobacterium paratuberculosis is an obligate pathogen; that is, it cannot multiply outside the cells of animals. It is known to be present in a wide variety of animals, including primates and humans. The best-studied animal paratuberculosis is bovine Johne's disease (BJD), a disease that causes chronic **diarrhea**, weight loss, and malnutrition in cattle and affects up to 25% of the dairy cattle in the United States. Cows infected with BJD are known to secrete Mycobacterium paratuberculosis in their milk, which is not destroyed by standard milk pasteurization methods, but only by ultrapasteurization. This bacterium has also been cultured from a municipal water supply in the United States.

SUMM A further object is to provide a composition and method for **treating** patients shown by the screening method to be infected with Mycobacterium paratuberculosis.

SUMM These objects and others are attained by the present invention, a composition and associated methods for detecting and **treating** a M. para. infection such as Crohn's disease in a human and for predicting a genetic predisposition thereto.

SUMM An embodiment of the **treatment** composition of the present invention comprises at least one antibiotic effective in the eradication of M. paratuberculosis.

SUMM In an embodiment of the **treatment** method, the effective antibiotic is administered to a patient having been found positive for M. paratuberculosis by the serologic method of the invention.

DETD The data also support an improved serologic kit comprising the composition of the invention to provide earlier diagnosis and better **treatment** of Crohn's disease.

DETD With the indication that Crohn's disease is at least in part caused by the presence of M. paratuberculosis, a **treatment** regimen including an administration of antituberculosis drugs was proposed. However, this bacterium is known to be resistant to most of these drugs. An in vitro study was performed to evaluate seven anti-TB drugs against M. para. isolated from resected tissue of CD patients using the Bactec system, which is known in the art, and the results are given in Table 2.

DETD Twenty-nine CD patients who tested serologically positive for M. para. were selected for rifabutin and macrolide antibiotic therapy (RMAT) for a duration of 6 months to 1 year based upon their overall response to the **treatment**. The regimen included 250 mgm po bid clarithromycin, 150 mgm 1 po bid rifabutin, and 200 mgm po qd of a probiotic containing equal amounts of Lactobacillus acidophilus and Lactobacillus rhamnosus.

DETD After 3 months all the patients were assessed to determine overall response to the **treatment**. 28% (8/29) of the patients achieved a state of clinical remission (as defined by the CDAI criteria with a score <150) while being off all other medications. The majority of these patients had acute presentation of CD when placed on RMAT. 31% (9/29) of the patients were not in clinical remission but experienced significant improvements as they discontinued the use of all other Crohn's medications. 28% (8/29) of the patients noticed some improvements on

RMAT but were still using traditional medications, such as sulfasalazine and corticosteroids. 14% (4/29) were nonresponders, since they were unable to tolerate the RMAT medications and discontinued therapy. These findings support the use of RMAT in the **treatment** of CD.

DETD The patient demonstrated significant healing (80%) of an ulcer seen in the ileum by endoscopy following a regimen of 250 mg clarithromycin twice a day and 150 mg rifabutin daily. The patient became asymptomatic in 2 weeks, and a followup endoscopy was performed after completing 1 month of **treatment**. The 4-cm ulcer had reduced in size to 1 cm, with excellent reepitheliazation from the edge of the ulcer inward. The remaining ileum to 120 cm was normal. The patient has remained symptom-free and continues on the antibiotic regimen.

DETD As this study was continued, 35 patients with CD were being **treated** with RMAT. 37% (13/35) of the patients developed a serum sickness-like illness during the first 4-6 weeks of **treatment**. The patients experienced flu-like symptoms such as fever, chills, moderate to severe arthralgia, back pain, anorexia, and **fatigue** . These symptoms generally lasted for a full week and dissipated over the following 3 weeks. With each patient, a majority of symptoms stopped within the first month of **treatment**. It was also found that these symptoms responded well to Cox-2 inhibitors (**celecoxib** --200 mgm po qd) with no adverse effects or worsening of colitis noted during **treatment**. These observations suggest that the Cox-2 inhibitors may help in controlling the initial side effects of RMAT. It is also thought that this serum sickness may be a Jarisch-Herxheimer reaction in response to the antimicrobial therapy.

DETD Current hypotheses are being investigated regarding the causative agent(s) of Crohn's disease. While many workers in the field have become convinced of the involvement of M. para., it may well turn out that this bacterium is but one of a number of pathogenic agents. Therefore, the regimen proposed herein preselects patients for antibiotic **treatment** by the detecting method of the present invention, the combined p35/p36 serological test, patients testing negative for M. para. being less likely to experience alleviation of CD symptoms under the antibiotic regimen.

DETD It may be appreciated by one skilled in the art that additional embodiments may be contemplated, including other recombinant clones chosen from the M. paratuberculosis genomic library and other antibiotic regimens for the **treatment** of bacteria-positive CD patients.

ACCESSION NUMBER: 2001:167903 USPATFULL

TITLE: Crohn's disease diagnostic and **treatment** methods and compositions

INVENTOR(S): Shafran, Ira, 1316 Greencove Rd., Winter Park, FL, United States 32789

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6297015	B1	20011002
APPLICATION INFO.:	US 1999-404095		19990923 (9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 1998-101579P	19980924 (60)

DOCUMENT TYPE: Utility

FILE SEGMENT: GRANTED

PRIMARY EXAMINER: Le, Long V.

ASSISTANT EXAMINER: Cook, Lisa V

LEGAL REPRESENTATIVE: Allen, Dyer, Doppelt, Milbrath & Gilchrist, P.A.

NUMBER OF CLAIMS: 3

EXEMPLARY CLAIM: 1

LINE COUNT: 362

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

n complex to the antigen
composition, wherein the bound antibody-antigen complex detects a presence of Mycobacterium avium ss. paratuberculosis, and thus indicates a presence of Crohn's disease; administering a regimen of an antibiotic effective in and sufficient for eradicating a presence of Mycobacterium paratuberculosis; and administering a regimen of a probiotic and a specific carbohydrate diet.

9. The method recited in claim 1, further comprising the steps, following the administering step, of: determining whether a **treated** patient is experiencing a serum sickness-like illness; and if the determining step is positive, **treating** the patient with a Cox-2 inhibitor.

10. The method recited in claim 9, wherein the Cox-2 inhibitor comprises **celecoxib**.

11. The method recited in claim 10, wherein the **celecoxib** is administered in an oral dose of 200 mgm once per day.

12. A method for **treating** a human patient suspected of having Crohn's disease comprising the steps of: screening for Crohn's disease by performing an ELISA analysis for serum antibodies to Mycobacterium avium subspecies paratuberculosis (MAP); and for patients screening positive for MAP, administering a regimen of an antibiotic effective in and sufficient for eradicating a presence of Mycobacterium paratuberculosis.

IT 54-85-3, Isoniazid 57-92-1, Streptomycin, biological studies 74-55-5, Ethambutol 98-96-4, Pyrazinamide 8063-07-8, Kanamycin 13292-46-1, Rifampicin 72559-06-9, Rifabutin 81103-11-9, Clarithromycin **1695 90-42-5**, Celecoxib
(antibiotic-based Crohn's disease treatment method, and Mycobacterium avium paratuberculosis-based diagnostic method)

ACCESSION NUMBER: 2002:336847 USPATFULL
TITLE: Crohn's disease **treatment** methods
INVENTOR(S): Shafran, Ira, Winter Park, FL, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002192201	A1	20021219
APPLICATION INFO.:	US 2002-165034	A1	20020607 (10)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 2001-968681, filed on 1 Oct 2001, PENDING Continuation-in-part of Ser. No. US 1999-404095, filed on 23 Sep 1999, GRANTED, Pat. No. US 6297015

	NUMBER	DATE
PRIORITY INFORMATION:	US 1998-101579P	19980924 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Jacqueline E. Hartt, Allen, Dyer, Doppelt, Milbrath & Gilchrist, P.A., 255 South Orange Avenue, Suite 1401, P.O. Box 3791, Orlando, FL, 32802-3791
NUMBER OF CLAIMS: 19
EXEMPLARY CLAIM: 1
LINE COUNT: 465
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

n complex to the antigen
composition, wherein the bound antibody-antigen complex detects a presence of Mycobacterium avium ss. paratuberculosis, and thus indicates a presence of Crohn's disease; administering a regimen of an antibiotic effective in and sufficient for eradicating a presence of Mycobacterium paratuberculosis; and administering a regimen of a probiotic and a specific carbohydrate diet.

9. The method recited in claim 1, further comprising the steps, following the administering step, of: determining whether a **treated** patient is experiencing a serum sickness-like illness; and if the determining step is positive, **treating** the patient with a Cox-2 inhibitor.

10. The method recited in claim 9, wherein the Cox-2 inhibitor comprises **celecoxib**.

11. The method recited in claim 10, wherein the **celecoxib** is administered in an oral dose of 200 mgm once per day.

12. A method for **treating** a human patient suspected of having Crohn's disease comprising the steps of: screening for Crohn's disease by performing an ELISA analysis for serum antibodies to Mycobacterium avium subspecies paratuberculosis (MAP); and for patients screening positive for MAP, administering a regimen of an antibiotic effective in and sufficient for eradicating a presence of Mycobacterium paratuberculosis.

IT 54-85-3, Isoniazid 57-92-1, Streptomycin, biological studies 74-55-5, Ethambutol 98-96-4, Pyrazinamide 8063-07-8, Kanamycin 13292-46-1, Rifampicin 72559-06-9, Rifabutin 81103-11-9, Clarithromycin **1695 90-42-5**, Celecoxib
(antibiotic-based Crohn's disease treatment method, and Mycobacterium avium paratuberculosis-based diagnostic method)

ACCESSION NUMBER: 2002:336847 USPATFULL
TITLE: Crohn's disease **treatment** methods
INVENTOR(S): Shafran, Ira, Winter Park, FL, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002192201	A1	20021219
APPLICATION INFO.:	US 2002-165034	A1	20020607 (10)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 2001-968681, filed on 1 Oct 2001, PENDING Continuation-in-part of Ser. No. US 1999-404095, filed on 23 Sep 1999, GRANTED, Pat. No. US 6297015

	NUMBER	DATE
PRIORITY INFORMATION:	US 1998-101579P	19980924 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Jacqueline E. Hartt, Allen, Dyer, Doppelt, Milbrath & Gilchrist, P.A., 255 South Orange Avenue, Suite 1401, P.O. Box 3791, Orlando, FL, 32802-3791
NUMBER OF CLAIMS: 19
EXEMPLARY CLAIM: 1
LINE COUNT: 465
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

14. The method recited in claim 13, wherein the Cox-2 inhibitor comprises **celecoxib**.

15. The method recited in claim 13, wherein the **celecoxib** is administered in an oral dose of 200 mgm once per day.

ACCESSION NUMBER:	2002:198264 USPATFULL		
TITLE:	Crohn's disease **treatment** methods		
INVENTOR(S):	Shafran, Ira, Winter Park, FL, UNITED STATES		
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002106357	A1	20020808
APPLICATION INFO.:	US 2001-968681	A1	20011001 (9)
	NUMBER		DATE
PRIORITY INFORMATION:	US 1998-101579P		19980924 (60)
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	APPLICATION		
LEGAL REPRESENTATIVE:	Allen, Dyer, Doppelt, Milbrath & Gilchrist, P.A., 255 South Orange Avenue, Suite 1401, P.O. Box 3791, Orlando, FL, 32802-3791		
NUMBER OF CLAIMS:	15		
EXEMPLARY CLAIM:	1		
LINE COUNT:	380		

-cyclooxygenase 2 inhibitor
antiangiogenic combination for treatment of cancer)

ACCESSION NUMBER: 2002:192070 USPATFULL

TITLE: Antiangiogenic combination therapy for the **treatment** of cancer

INVENTOR(S): McKearn, John P., Wildwood, MO, UNITED STATES
Gordon, Gary B., Highland Park, IL, UNITED STATES
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Gately, Stephen T., Palatine, IL, UNITED STATES
Koki, Alane T., Beaufort, MO, UNITED STATES
Masferrer, Jaime L., Ballwin, MO, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002103141	A1	20020801
APPLICATION INFO.:	US 2001-843132	A1	20010425 (9)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1999-470951, filed on 22 Dec 1999, PENDING

	NUMBER	DATE
PRIORITY INFORMATION:	US 1998-113786P	19981223 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Pharmacia Corporation, Corporate Patent Department, P.O. Box 5110, Chicago, IL, 60680-9889
NUMBER OF CLAIMS: 181
EXEMPLARY CLAIM: 1
LINE COUNT: 8069
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

and/or an effective amount of indomethacin. Of these two, metronidazole is preferred. The present invention is further directed to methods of **treating** smooth muscle contraction, including the contraction of the uterus during, for instance, premature labor. The methods include administering a composition to a subject who has or is at risk of developing smooth muscle contractions a composition comprising an amount of a heterocycle-containing compound effective to prevent, or control by extending to substantially full-term, a premature labor. The heterocycle-containing compound present in the composition is a diphenyl heterocycle derivative, a prostaglandin analog, or a combination thereof.

DETD [0076] The present invention is also directed to methods for modifying inflammatory responses that are mediated by PGE.sub.2. Prostaglandins, for instance PGE.sub.2, and leukotrienes (for instance LTB.sub.4), are known to arise during inflammation. In high levels, PGE.sub.2 is pro-inflammatory because it stimulates synthesis of IL-8, while in low levels, it can be cytoprotective, because of its capacity to stimulate cytokine IL-10 production. The latter cytokine (IL-10) downregulates inflammation, while the former (IL-8) signals the infiltration of polymorphonuclear neutrophils (a type of leukocyte) into the affected tissue. PGE.sub.2 is typically produced by a cell, for instance a damaged cell, is released by the cell and interacts with a receptor on a second cell. The second cell may be a leukocyte whose function is to release substances toxic for microorganisms. These substances include reactive oxygen species (including free hydroxyls, superoxide anion, and singlet oxygen), proteolytic enzymes, and acids. While toxic to microorganisms, they are also very toxic for the host's own tissues. It is expected that the prostaglandin analogs of the present invention, preferably PGE.sub.2-imidazole or PGE.sub.2-histidine, will bind to PGE.sub.2 receptors and inhibit the binding of PGE.sub.2, and possibly other prostaglandins. It is further expected that the binding of PGE.sub.2-imidazole or PGE.sub.2-histidine to a PGE.sub.2 receptor will not cause a response in the cell that includes the receptor. Examples of conditions that can be **treated** by modifying inflammatory responses that are mediated by PGE.sub.2 include, for instance, colibacillosis and mastitis in cattle, pancreatitis, Barrett's esophagus, gastroesophageal reflux disease syndrome (GERDS), and hepatitis.

DETD [0111] Considering that purified PGE.sub.2-imidazole inhibited cAMP formation in CT-stimulated CHO cells (FIG. 4), the capacity of this adduct to block CT-induced fluid accumulation in murine intestinal loops was tested. FIG. 5A shows that PGE.sub.2-imidazole, in doses as low as 100 .mu.g, instilled into the intestinal lumen significantly reduced CT-induced fluid accumulation. A dose of 200 .mu.g completely blocked fluid loss following CT challenge during the 6-hour observation period. The cAMP levels (FIG. 5B) in the intestinal loop fluids were markedly reduced by PGE.sub.2-imidazole **treatment** and coincided with the reduction in fluid accumulation.

DETD [0122] Mouse intestinal loops challenged with CT and dosed with L-histidine accumulated significantly less fluid than those from the corresponding CT-challenged control mice (FIG. 1). Generally, the observed dose of L-histidine, providing mouse intestinal loops with maximum protection against CT-induced fluid accumulation, was relatively large (592 mg/kg), even when **treatment** was initiated at the same time as toxin challenge (FIG. 1).

DETD [0124] L-histidine was demonstrated to react chemically with PGE.sub.2 (FIG. 3), and we considered the possibility that L-histidine inhibited the action of PGE.sub.2 in murine intestinal loops challenged with CT. It was demonstrated that the purified PGE.sub.2-imidazole adduct reduced cAMP levels in culture supernatants of CHO cells stimulated with CT (FIG. 4). It was surmised that L-histidine, as well as the PGE.sub.2-imidazole adduct, interfered with the activity of PGE.sub.2 in the CT-**treated** cells. It was not possible to measure the reduction of PGE.sub.2 in vivo or in vitro by PGE.sub.2-specific

radioimmunoassays, since the PGE.sub.2-histidine (or imidazole) adduct appeared to react equally well with antibodies to PGE.sub.2. In part, L-histidine could have served as a PGE.sub.2-inactivating compound, which provided additional support for the role of PGE.sub.2 in CT-induced secretion of water and electrolytes in the small intestine. Additionally, the PGE.sub.2-histidine covalent adduct could serve to inhibit the potential of PGE.sub.2 to stimulate adenylate cyclase. Indeed, purified PGE.sub.2-imidazole adduct inhibited CT-induced fluid accumulation in murine intestinal loops (FIG. 5A). In this case, the imidazole moiety may inactivate the native stimulatory effect of PGE.sub.2 on ion transport, but it is likely the structural similarity of the PGE.sub.2-adduct to PGE.sub.2 that enables it to interfere with the action of CT-induced PGE.sub.2 and fluid accumulation. Other PGE.sub.2 analogs (e.g., PGA.sub.2 and PGB.sub.2) also reduce CT-induced fluid accumulation in murine intestinal loops with lower potency.

DETD [0130] Adult female Swiss-Webster mice (25-30 g) were purchased from Taconic Farms, Inc. (Germantown, N.Y.) and housed in a specific pathogen-free animal facility at UTMB in Galveston, Tex. Mice were fasted for 18 hr before surgery to reduce the food content of the small intestine. A ventral midline incision was made under ether anesthesia to expose the small intestine. A single 5-cm segment of small intestine, ligated with "00" silk suture, was injected with 1 .mu.g of cholera toxin (CT) in 100 .mu.l. After 6 hours observation, the animals were euthanized by cervical dislocation and the intestinal loops were removed. The amount of luminal fluid was measured and expressed as .mu.l/cm, while the tissue was prepared for light or electron microscopy. In some experiments, intestinal challenge was accomplished by injecting 100 .mu.g of CT followed immediately with 160 .mu.g/100 .mu.l **celecoxib** (dissolved in 3% dimethylsulfoxide in phosphate buffered saline) at the time of challenge. Fluid volume was measured 6 hours after challenge. Specimens of fluid and tissue were collected at time of necropsy.

DETD [0131] The inhibitory effect on CT-induced fluid accumulation was observed with dosages of **celecoxib** reported to be specific for COX-2.

DETD [0133] FIG. 11 shows that CT-induced fluid accumulation in murine intestinal loops is significantly reduced by **celecoxib**.

DETD [0142] The results indicate that **celecoxib**, PGE.sub.2-histidine, and imidazole each inhibit adenylate cyclase enzyme activity (FIG. 12). The data in FIG. 12 also show the absence of adenylate cyclase inhibition by SC560 and **rofecoxib** under the conditions tested. FIG. 13 shows that SC560 inhibits cholera toxin-induced fluid secretion, although it has not been demonstrated that it does so by inhibiting adenylate cyclase under the conditions tested (FIG. 12). **Rofecoxib** does not inhibit cholera toxin-induced secretion under the conditions tested. **Celecoxib** was designed to be a highly specific inhibitor of cyclooxygenase-2 (COX-2). The mechanism by which **celecoxib** inhibits adenylate cyclase is not known; however, it was observed that imidazole also inhibits adenylate cyclase. Since imidazole is part of the chemical structure of **celecoxib**, it is suspected that this moiety participates in the functional activity of inhibiting adenylate cyclase. Imidazole is known to bind divalent cations (e.g., Mg.sup.++, Zn.sup.++, and Ca.sup.++), and these metal cations are known to be required for adenylate cyclase activity. In fact, a recent report in which the X-ray crystallography-derived structure of rat adenylate cyclase was determined showed that there were two binding domains in the catalytic site of adenylate cyclase divalent cations (Zn.sup.++ and Mg.sup.++). We suspect that the imidazole group of **celecoxib** is enabling the drug to bind to the metal ions in the enzyme's active site, which would block the substrate (ATP) from entering. The end result would be inhibition of adenylate cyclase activity. From a physiological perspective in the small intestine, such an inhibitor would reduce or block cholera toxin-induced fluid loss (**diarrhea**).

DETD [0145] The adenylate cyclase enzyme assay was performed as described earlier in Example 1; however, the assay was used to assay various inhibitors (e.g., PGE.sub.2-histidine, **celecoxib**, and imidazole). The amount of enzyme in each experiment was 0.46 nmole, and the concentration of each inhibitor was varied in order to determine the dose that would block 50% of the enzyme activity (IC.sub.50).

DETD [0147] The results summarized in the FIGS. 14-16 indicate that adenylate cyclase can be inhibited, which forms a strategy for reducing or blocking intestinal fluid secretion induced by several agents of diarrheal disease. FIG. 14 shows the dose response for PGE.sub.2-histidine in inhibiting adenylate cyclase. The IC.sub.50 dose of PGE.sub.2-histidine inhibiting 50% of the enzyme activity (0.46 nmole) was 21.5 .mu.mole. FIG. 15 shows that when a similar experiment was performed with **celecoxib**, and its IC.sub.50 dose was 20 mmole. FIG. 16 shows that imidazole alone exhibited inhibited adenylate cyclase activity; however, it was less potent (IC.sub.50=1.57 mmole). Table 1 summarizes the inhibitory potencies of the various adenylate cyclase inhibitors. Similar results were observed when edema factor from B. acthracis was used as the adenylate cyclase.

TABLE 1

Molar concentration of commonly available drugs required to inhibit Adenylate Cyclase

Enzyme:Drug	Ratio
Adenylate Cyclase:**Celecoxib**	0.46 nm:20.0 .mu.m
Adenylate Cyclase:Imidazole	0.46 nm:1.57 mm
Adenylate Cyclase:Histidine:PGE.sub.2 Adduct	0.46 nm:21.5 .mu.m

CLM What is claimed is:

8. The method of claim 6 wherein the diphenyl heterocycle derivative is **celebrex** or DuP-697.

16. The method of claim 15 wherein the diphenyl heterocycle derivative is **celebrex** or DuP-697.

24. A method for **treating** intestinal fluid loss in a subject, the method comprising administering to a subject who has or is at risk of developing intestinal fluid loss a composition comprising an effective amount of a heterocycle derivative selected from the group consisting of a diphenyl heterocycle derivative, a prostaglandin analog, and a combination thereof, wherein the fluid loss is not associated with a pathogen polypeptide having ADP-ribosylation activity.

35. A method for **treating** intestinal fluid loss in a subject, the method comprising administering to a subject who has or is at risk of developing intestinal fluid loss a composition comprising an effective amount of a heterocycle-containing compound, wherein the intestinal fluid loss is associated with a pathogen polypeptide having ADP-ribosylation activity.

43. The method of claim 35 wherein the heterocycle derivative is not **celecoxib**.

47. A method for **treating** whooping cough in a subject, the method comprising administering to a subject who has or is at risk of developing whooping cough a composition comprising an effective amount of an heterocycle-containing compound.

55. A method for **treating** anthrax in a subject, the method comprising administering to a subject who has or is at risk of developing anthrax a composition comprising an effective amount of a heterocycle-containing compound.

IT 53-86-1, Indomethacin 71-00-1, L-Histidine, biological studies
288-32-4, Imidazole, biological studies 443-48-1, Metronidazole
88149-94-4 **162011-90-7 169590-42-5** 188817-13-2
(heterocycle derivs. for inhibiting adenylate cyclase and methods of use for treating intestinal fluid loss and whooping cough and anthrax and conditions assocd. with smooth muscle contraction)

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TI Crohn's disease diagnostic and **treatment** methods and compositions
AB A composition and method for detecting Crohn's disease include the use of serological testing as a rapid and simple way to diagnose Crohn's disease. The serological tests were based on the use of the two recombinant clones isolated from an M. paratuberculosis genomic library that expressed 35K and 36K MW antigens. Antigen p35 was isolated from Johne's disease sera (acid-fast bacilli form) and p36, from human CD sera (spheroplast form). The combined use of p35 and p36 recombinant antigens provides a highly specific and sensitive test to demonstrate the humoral immune response of CD patients to M. paratuberculosis. A serologic kit is disclosed including the composition including the combined p35 and p36 antigens. A **treatment** methodology utilizes antimycobacterial drugs, preferably upon patients prescreened for the presence of M para. A particular antibiotic regimen includes an administration of both rifabutin and clarithromycin, which has been found to be particularly effective in alleviating the symptoms of Crohn's disease.
SUMM The present invention relates to compositions and methods for diagnosing and **treating** Crohn's disease, and, more particularly, to such compositions and methods for screening for a presence of a bacterium believed involved in causing Crohn's disease and for **treating** patients shown by the screening method to be infected with the bacterium.

SUMM Common symptoms of Crohn's disease include abdominal pain and **diarrhea**. There may also be **rectal bleeding**, weight loss, and fever. The bleeding may be serious and persistent, leading to anemia. Children may suffer delayed development and stunted growth.